VNiVERSiDAD D SALAMANCA

FACULTAD DE FARMACIA

DEPARTAMENTO DE CIENCIAS FARMACÉUTICAS

Tesis Doctoral

Monitorización farmacocinética de anti-TNF para la personalización de la terapia en enfermedad inflamatoria intestinal

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2020

Los abajo firmantes, **Dra María Victoria Calvo Hernández**, Profesora Asociada del Departamento de Ciencias Farmacéuticas de la Universidad de Salamanca, Directora de la presente Tesis; la **Dra Noemí Rebollo Díaz**, Profesora Asociada del Departamento de Ciencias Farmacéuticas de la Universidad de Salamanca, Directora de la presente Tesis y la **Dra Ana Martín Suarez**, Profesora Titular del Departamento de Ciencias Farmacéuticas de la Universidad de Salamanca, Tutora de la presente Tesis.

CERTIFICAN QUE:

La Tesis Doctoral realizada por compendio de publicaciones titulada: **"Monitorización farmacocinética de anti-TNF para la personalización de la terapia en enfermedad inflamatoria intestinal"**, realizada en el Complejo Asistencial Universitario de Salamanca bajo nuestra dirección por el Graduado en Farmacia **José Germán Sánchez Hernández**, consideran concluido el trabajo y autorizan su presentación a fin de que pueda ser juzgado por el Tribunal correspondiente.

Y para que así conste, firman el presente certificado en Salamanca, a 30 de mayo de 2020.

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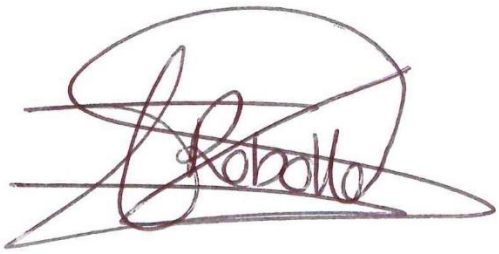

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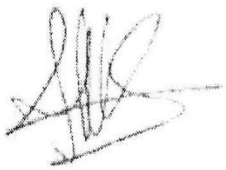

Fdo: Dra Ana Martín Suarez

AGRADECIMIENTOS

En estas líneas me gustaría agradecer a todas las personas que de diferentes maneras han colaborado en la realización de mi Tesis Doctoral.

A mis dos directoras de Tesis, Dra María Victoria Calvo Hernández y Dra Noemí Rebollo Díaz, por su entrega y dedicación, sus buenos consejos, su cariñoso trato y sus ánimos.

A mi tutora de Doctorado, Dra Ana Martín Suarez, por su dedicación y amabilidad.

A todo el equipo médico y de enfermería de la Unidad de Enfermedad Inflamatoria Intestinal del Complejo Asistencial Universitario de Salamanca, en especial a los doctores Dr Antonio Rodríguez, Dr Fernando Muñoz, Dra Vanessa Prieto, Dra Alejandra Fernández y Dra María Concepción Piñero, por la confianza depositada en mí, el conocimiento clínico que me habéis trasmitido y la amable disponibilidad.

Al personal del Departamento de Ciencias Farmacéuticas de la Universidad de Salamanca, en especial al Dr Jonás Samuel Pérez Blanco, por trasmitirme sus conocimientos y por su dedicación desinteresada.

A mis compañeros del Servicio de Farmacia del Complejo Asistencial Universitario de Salamanca, por su amistad y compañerismo, por su ayuda inestimable y por su apoyo desinteresado. Gran parte de este trabajo es gracias a vosotros.

A mis padres por su apoyo, comprensión e interés.

A Eva, mi compañera de viaje. Gracias por todo.

A todos vosotros muchísimas gracias.

PREFACIO

La presente Tesis Doctoral corresponde a un compendio de trabajos previamente publicados que se especifican a continuación:

I. **Sánchez-Hernández JG**, Rebollo N, Muñoz F, Martin-Suarez A, Calvo MV. Therapeutic drug monitoring of tumour necrosis factor inhibitors in the management of chronic inflammatory diseases. Annals of Clinical Biochemistry. 2019; 56(1): 28-41.

Factor de Impacto (JCR): 1,893, Cuartil: 3, Ranking: 17/29 (medical laboratory technology).

DOI: 10.1177/0004563218782286.

II. **Sánchez-Hernández JG**, Pérez-Blanco JS, Rebollo N, Muñoz F, Prieto V, Calvo MV. Biomarkers of disease activity and other factors as predictors of adalimumab pharmacokinetics in inflammatory bowel disease [published online ahead of print, 2020 May 19]. European Journal of Pharmaceutical Sciences. 2020; 150: 105369.

Factor de Impacto (JCR): 3,532, Cuartil: 1, Ranking: 35/276 (pharmacology and toxicology).

DOI: 10.1016/j.ejps.2020.105369

III. **Sánchez-Hernández JG,** Rebollo N, Martin-Suarez A, Calvo MV, Muñoz F. A 3-year prospective study of a multidisciplinary early proactive therapeutic drug monitoring programme of infliximab treatments in inflammatory bowel disease. British Journal of Clinical Pharmacology. 2020; 86(6): 1165-1175.

Factor de impacto (JCR): 3,867, Cuartil: 1, Ranking: 57/267 (pharmacology and pharmacy).

DOI: 10.1111/bcp.14229

ÍNDICE GENERAL

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I. INTRODUCCIÓN

1. Enfermedad inflamatoria intestinal

La enfermedad inflamatoria intestinal (EII) es un proceso crónico caracterizado por una respuesta inmune desproporcionada que daña los tejidos del tracto digestivo y provoca lesiones de diferente gravedad. La colitis ulcerosa (CU) y la enfermedad de Crohn (EC) son las formas más comunes de EII[1,2]. Estas patologías comparten muchas similitudes en términos de síntomas, factores de riesgo y tratamiento, siendo la principal diferencia el área del sistema digestivo donde se produce la inflamación. Así, en la CU solo se ve afectada la mucosa del intestino grueso en extensión variable, mientras que la EC es un proceso inflamatorio que puede afectar a cualquier segmento del tracto digestivo, desde la boca hasta el ano. La EII incluye también otras patologías de menor prevalencia como la "colitis inclasificada" y la "colitis indeterminada". La primera afecta al colon y comparte características de EC y CU mientras que el término "colitis indeterminada" se reserva a aquella EII intervenida quirúrgicamente en las que sea imposible clasificarlas como EC o CU[1,2].

Una característica diferencial de la EC respecto a la CU es la afectación inflamatoria segmentaria, presentando áreas de intestino sanas entre segmentos afectados. Las regiones anatómicas donde con mayor frecuencia se presenta la EC son el íleon, colon y región perianal[2]. En la CU la inflamación afecta exclusivamente a la mucosa, mientras que en la EC puede extenderse hasta la serosa, es lo que se conoce como afectación transmural. La EC frecuentemente se asocia con el desarrollo de complicaciones durante el curso evolutivo de la enfermedad, como son la aparición de estenosis, fístulas y abscesos.

Los principales signos y síntomas asociados a la EII incluyen dolor abdominal, fiebre, incontinencia fecal, sangrado rectal, pérdida de peso y fatiga. En el transcurso de la EII hay una alternancia de episodios de actividad clínica de diferente intensidad denominados brotes, con otros de inactividad o quiescencia denominados episodios de

remisión[3,4]. Además, pueden presentarse síntomas en localizaciones extradigestivas, siendo las más frecuentes la piel, las articulaciones, la vía biliar y los ojos[5]. Por otra parte, debido al curso evolutivo recurrente y a la cronificación, pueden desarrollarse complicaciones como obstrucciones intestinales, fistulas (fundamentalmente en EC), y los pacientes presentan un mayor riesgo que la población general de desarrollar cáncer de colon[6].

Las manifestaciones endoscópicas características de la EC incluyen eritema, mucosa con aspecto empedrado, friabilidad mucosa, úlceras y estenosis. En el 50% de los pacientes se observa compromiso ileocólico, en el 30% la afectación se encuentra limitada a intestino delgado y en el 20% las lesiones se limitan al colon exclusivamente[,7,8].

A diferencia de la EC, en la CU se observa una inflamación continua de la mucosa del colon y se presenta habitualmente sin granulomas en la biopsia[1]. La afectación rectal se manifiesta prácticamente siempre y desde esta región se extiende en sentido ascendente y de forma continua, sin tramos intermedios no afectados ni mucosa sana interlesional. La aparición de fístulas, estenosis o engrosamientos transmurales es excepcional. Endoscópicamente la mucosa del colon presenta una apariencia granular, con pérdida del patrón vascular, eritema difuso, ulceraciones habitualmente superficiales de pequeño tamaño aunque en casos graves pueden llegar a ser úlceras grandes y profundas con exudado y hemorragia.

La EII en la infancia es una patología de incidencia creciente en los últimos años[9]. En este grupo de edad predomina la CU o colitis inclasificada, mientras que la prevalencia de la EC va aumentando con la edad[9]. Las afecciones suelen ser más extensas que en la edad adulta, siendo la pancolitis y la EC ileo-colónica los tipos de EII más prevalentes. Además, existe mayor afectación del tracto digestivo alto (gastroduodenal) y evolucionan a formas complicadas más frecuentemente. Estas afecciones presentan

características propias en la infancia, como la mayor agresividad de la enfermedad, mayores manifestaciones extraintestinales, mayor componente genético, pero sobre todo cabe destacar la repercusión sobre el crecimiento, la maduración ósea y el estado nutricional del niño[10,11].

1.1 Epidemiología

La EII afecta particularmente a adultos de mediana edad que se encuentran en una etapa vital en la que están desarrollando su formación académica, profesional y familiar. Por ello, se trata de una enfermedad que impacta notablemente en la calidad de vida de los pacientes.

Desde el punto de vista geográfico la incidencia de la EII varía ampliamente, encontrándose las mayores cifras en las naciones más industrializadas de occidente, como son las regiones de América del Norte y Europa[12]. Sin embargo, se está observando un aumento de la incidencia epidemiológica en todo el mundo, especialmente en aquellas regiones en desarrollo[13,14]. En Europa, las tasas de incidencia más elevadas corresponden a los países de norte (países escandinavos, Reino Unido...), sin embargo, en las últimas décadas las diferencias con los países mediterráneos se han acortado[12,15].

Aunque con alguna limitación metodológica, se ha descrito una incidencia creciente y progresiva de EII en adultos en nuestro país, especialmente la de la EC[16-20]. Durante la última década, se ha estimado una incidencia entre 5,9 y 10,8 nuevos casos cada 100.000 habitantes por año para la EC y entre 7,1 y 9,6 para la CU[16-20]. En el reciente estudio EpidemIBD, el más amplio publicado hasta la fecha en nuestro país, se estima la incidencia anual de EII en 14,3 nuevos casos por 100.000 habitantes (6,5 en EC, 7,1

en CU y 0,9 en colitis inclasificada)[17]. La prevalencia de EC y CU se estima en 137,17 y 99,84 por 100.000 habitantes, respectivamente[21].

La incidencia de la EII en la edad pediátrica se encuentra así mismo en ascenso progresivo en los últimos años con 5-7 nuevos casos por cada 100.000 habitantes[22]. Un tercio de los casos de EII se diagnostican antes de los 20 años, la mayoría en los años de la adolescencia, mientras que solamente un 4% son diagnosticados antes de los 5 años[23,24].

1.2 Etiopatogenia

En la EII tiene lugar una alteración inmunológica en la interacción entre los antígenos intraluminales procedentes fundamentalmente de la flora microbiana intestinal y el sistema inmunitario local (tanto innato como adquirido), que pierde su habitual "actitud tolerante" frente al ecosistema microbiano.

Diversos estudios han identificado *loci* de susceptibilidad del genoma[25,26]. Cuando sobre esta base de predisposición genética coinciden diferentes factores ambientales, tienen lugar trastornos de la respuesta inmune innata como alteraciones de la mucosa intestinal, disfunción de las células de Paneth, anomalías con respuesta proteica defectuosa o fenómenos de autofagia, entre otros[27-32]. Por otro lado, también se han identificado deficiencias en la respuesta inmune adaptativa como desequilibrios entre linfocitos T efectores, reguladores, citoquinas implicadas en la respuesta inmune y alteraciones en la migración de leucocitos[30,32]. Por último, se ha observado una disbiosis y disminución de la diversidad de la microbiota comensal habitual del intestino[33]. La figura 1 muestra los principales mecanismos etiopatológicos que intervienen en la EII.

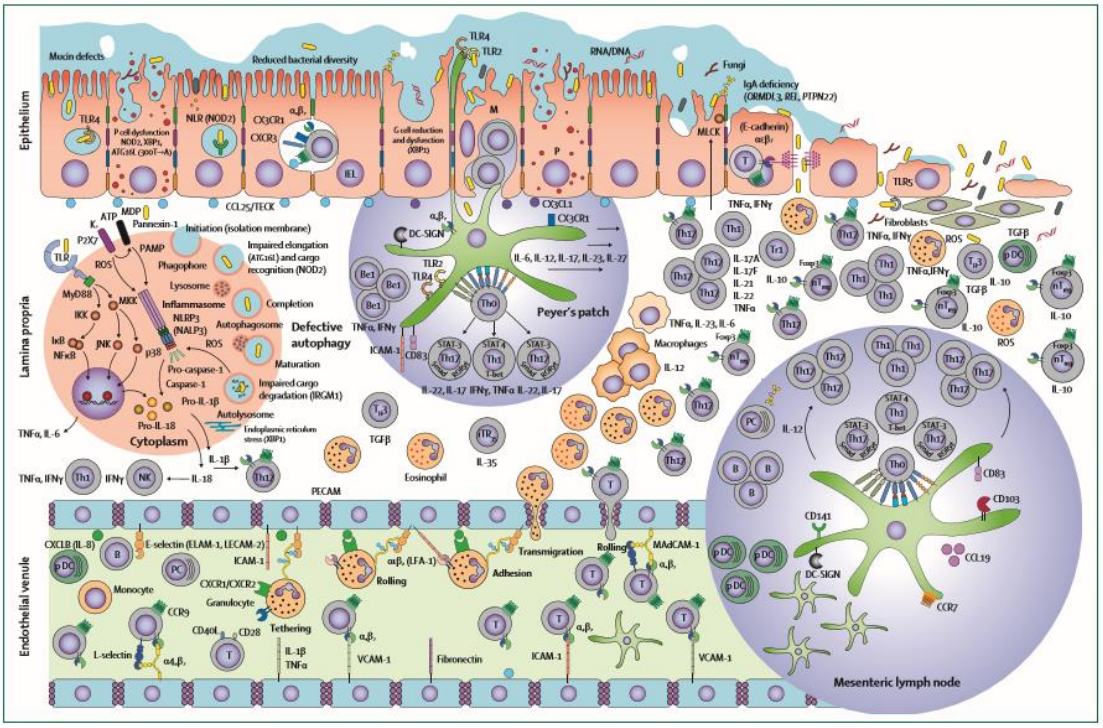

Figura 1. Esquema del sistema inmunológico intestinal en la enfermedad inflamatoria intestinal[34].

En relación a los factores ambientales, en los últimos años se han realizado diversos estudios que relacionan diferentes estilos de vida con la aparición de EII[35-37]. Un estilo de vida urbano, el sedentarismo, la contaminación ambiental y una dieta rica en azucares y grasas poliinsauradas se asocian con una mayor susceptibilidad de padecer EII. Sin embargo, el factor ambiental que ha demostrado tener una mayor relación con la aparición de esta patología es el tabaco[38,39]. De hecho, este hábito se ha relacionado con peor pronóstico de la enfermedad y rápida progresión[40,41]. Además, el hábito temprano del tabaco se ha asociado con un aumento en la probabilidad de desarrollar la enfermedad[41]. Por otra parte, con relativa frecuencia, la aparición de la EII ocurre después de una gastroenteritis infecciosa, como se ha descrito con *salmonella* y *campylobacter* , debido a una alteración de la flora bacteriana habitual de la mucosa digestiva (disbiosis)[42,43]. La localización de las lesiones coinciden con las zonas de

mayor abundancia de microbiota que además presentan abundancia de tejido linfoide, como las regiones entre las células que componen la mucosa intestinal (intramucosa)[27]. Todas estas circunstancias, provocan una interacción alterada de la microbiota comensal habitual, que normalmente convive en simbiosis con el huésped humano, así como cambios estructurales en la biopelícula que recubre la mucosa intestinal que forma parte de la primera línea de defensa del sistema inmunitario intestinal.

1.3 Diagnóstico

El diagnóstico de la EII debe basarse en una combinación de datos clínicos, de laboratorio, endoscópicos, radiológicos e histológicos[1,2]. En ocasiones se ve dificultado, sobre todo en la EC, porque los síntomas pueden ser inespecíficos y pueden confundirse con otras patologías como enfermedades infecciosas (parasitosis, colitis pseudomembranosa, colitis de origen bacteriano, etc), neoplasias, colitis de origen vascular, otras colitis inflamatorias (microscópica, colágena, actínica, etc.), diverticulosis, etc. Por lo tanto, el diagnostico diferencial de esta enfermedad puede demorarse en tiempo debido a la poca especificidad de su sintomatología.

La evaluación endoscópica es la prueba de referencia en el diagnóstico de la EII para detectar y medir la inflamación intestinal, pero es invasiva, costosa y molesta para el paciente. Las pruebas de imagen están indicadas para completar el estudio de extensión de la enfermedad y para descartar complicaciones asociadas. Además, existen parámetros analíticos o biomarcadores que son sencillos de realizar, seguros y de bajo coste, y que presentan buena correlación con la actividad endoscópica. Estas características hacen estas pruebas especialmente atractivas para el diagnóstico precoz y la monitorización de la EII, ahorrando un buen número de exploraciones endoscópicas y de imagen.

1.3.1 Clasificación de la enfermedad inflamatoria intestinal e índices de actividad

Una de las principales características de la EII es la marcada heterogeneidad de las manifestaciones clínicas y el pronóstico de la enfermedad, por este motivo se han realizado diferentes clasificaciones para facilitar el seguimiento y tratamiento de estas patologías. Actualmente se utiliza la clasificación de Montreal, recogida en las tablas 1 y 2, que se basa en la extensión de la inflamación, en la gravedad clínica y, en el caso de la EC, en el comportamiento evolutivo por su tendencia a la complicación (inflamatorio, estenosante, fistulizante o penetrante)[44].

Tabla 1. Clasificación de Montreal de la Enfermedad de Crohn

A: Edad de diagnóstico	A1: Menor de 16 años (inclusive) A2: Entre 17 y 40 años A3: Mayor de 40 años
L: Localización anatómica	L1: Ileo distal incluyendo, si se afecta, el ciego por continuidad L2: Cólonica L3: Ileocolónica L4: Tracto digestivo superior. Se añade a cualquiera de los 3 anteriores
B: Comportamiento (curso evolutivo)	B1: Patrón inflamatorio B2: Patrón estenosante B3: Patrón perforante (fistulizante) p: Enfermedad perianal (se añade a cualquiera de los anteriores)

Tabla 2. Clasificación de Montreal de la Colitis Ulcerosa

E: Extensión	E1: Proctitis ulcerativa (limitada a recto) E2: Colitis izquierda. Limitada a colon izquierdo, la lesión no supera el ángulo esplénico E3: Colitis extensa (pancolitis). Afectación proximal al ángulo esplénico
S: Gravedad	S0: Colitis en remisión. No hay síntomas. S1: Leve. Cuatro o menos deposiciones diarias con sangre, sin fiebre, leucocitosis y marcadores de inflamación normales S2: Moderada. Cinco o más deposiciones diarias, pero con mínimos signos de inflamación sistémica S3: Grave. Al menos 6 deposiciones diarias con sangre, fiebre (>37,5ºC), taquicardia (> 90 lpm), hemoglobina menor de 10,5 g/dL y velocidad de sedimentación globar (VSG) mayor de 30 mm/h

Para evaluar la actividad clínica de la EC y analizar la respuesta al tratamiento, se han desarrollado índices como el Crohn's Disease Activity Index (CDAI)[45] y el índice de Harvey Bradshaw (HBI)[46]. La tabla 3 muestra el HBI, el índice más utilizado en la práctica clínica debido a su menor complejidad y su buena correlación con el CDAI. Además, se han desarrollado índices de actividad endoscópica para evaluar la actividad de la EC, como el índice endoscópico de severidad (CDEIS) y el índice endoscópico simple para EC (SES-CD)[47,48].

Tabla 3. Índice de Harvey-Bradshaw para Enfermedad de Crohn

Parámetro	Puntuación
Estado general	0=bien; 1=ligeramente por debajo de lo normal; 2=malo; 3=muy malo; 3= terrible
Dolor abdominal	0= ausente; 1= ligero; 2= moderado; 3= intenso
Número de heces líquidas o blandas	Número de heces líquidas/blandas en 24 horas
Masa abdominal	Ninguna=0; dudosa=1; definida=2; definida y blanda = 3
Número de complicaciones (anotar 1 por cada ítem)	Artralgia Uveítis Eritema nudoso Úlcera aftosa Pioderma gangrenoso Estomatitis Fisura anal Abceso Nuevas fístulas
Remisión <5 Enfermedad leve 5-7 Enfermedad moderada 8-16 Enfermedad grave >16	

Análogamente, se han desarrollado índices para evaluar la gravedad de la actividad clínica de la CU, como el índice de actividad Truelove-Witts modificado o el índice de Mayo[49,50]. No obstante, debido a su complejidad, en la práctica clínica, se utilizan otros índices simplificados y más fáciles de implementar como el índice Mayo parcial mostrado en la tabla 4[51]. Además, para definir la gravedad del compromiso de la mucosa en la enfermedad se han utilizado varias clasificaciones endoscópicas, siendo las más

utilizadas la clasificación endoscópica de Mayo y el índice endoscópico de severidad en CU (UCEIS)[52,53].

Tabla 4. Índice de Mayo para la Colitis Ulcerosa

Parámetro	Puntuación			
	0	**1**	**2**	**3**
Frecuencia de evacuación	Normal para el paciente	1-2 veces lo normal	3-4 veces lo normal	≥5 veces lo normal
Sangrado rectal	No	Vetas (menos del 50% de las veces)	Sangrado obvio casi todo el tiempo	Paso de sangre únicamente
Hallazgos Endoscópicos	Inactiva	Friabilidad Leve	Friabilidad Moderada	Friabilidad Grave
Evaluación global del médico	Normal	Leve	Moderada	Grave
< 2	Remisión			
2 - 4	Actividad leve			
5 - 7	Actividad moderada			
> 7	Actividad grave			

1.3.2 Técnicas endoscópicas

La endoscopia digestiva es la herramienta básica para el manejo de la EII, tanto para su diagnóstico inicial como para controlar la respuesta al tratamiento. También, es útil para la vigilancia y el cribado de la displasia y/o cáncer colorrectal y, en algunos casos, permite tratar las complicaciones derivadas de la enfermedad como las estenosis o hemorragias.

La colonoscopia con ileoscopia es fundamental en el diagnóstico de pacientes con sospecha de EII. Ante un cuadro leve o moderado, se puede realizar la exploración con seguridad en todo el colon. Pero si el paciente presenta síntomas o signos de actividad grave, se debe realizar únicamente recto-sigmoidoscopia para minimizar el riesgo de perforación. La exploración endoscópica permite diferenciar entre los dos tipos de EII y determinar la extensión y gravedad de la actividad inflamatoria[54].

Existen también otras técnicas endoscópicas para el diagnóstico y seguimiento de la EC. La enteroscopia permite explorar el intestino delgado y sirve para el diagnóstico de la enfermedad, aunque para este fin ha quedado relegada por técnicas menos invasivas como la cápsula endoscópica. Entre las utilidades de esta herramienta destacan la toma de muestras en biopsias, el tratamiento de lesiones sangrantes y la dilatación de estenosis provocadas por la propia EC. La cápsula endoscópica es una herramienta que consiste en que el paciente ingiere una cámara, en forma de cápsula ovalada, que realiza fotogramas de todo el intestino[55]. Esta técnica permite evaluar fundamentalmente el intestino delgado siempre que el paciente no presente estenosis intestinal, ya que la cápsula podría quedar atrapada. Entre sus limitaciones destacan la dificultad para localizar las lesiones y la imposibilidad para realizar tratamiento o la toma de biopsias.

1.3.3 Marcadores bioquímicos

En la EII las alteraciones bioquímicas observadas con mayor frecuencia son anemia, trombocitosis y elevación de marcadores inflamatorios, como la Proteina C reactiva (PCR) y la Velocidad de sedimentación globular (VSG)[56,57]. En aquellos pacientes con compromiso extenso del intestino delgado es posible observar así mismo hipoalbuminemia y déficit de vitaminas. Los brotes leves no suelen mostrar alteraciones significativas en estos parámetros, al contrario de lo que ocurre en aquellos episodios

moderados o graves donde se suele observar anemia por déficit de hierro, hipoalbuminemia y elevación de parámetros inflamatorios[57].

Un marcador bioquímico de reciente introducción en la práctica clínica es la Calprotectina fecal (CF). Esta proteína constituye el 60% del contenido total de proteínas presentes en el citoplasma de los neutrófilos, y se encuentra en concentraciones elevadas en las heces de pacientes con diversos procesos inflamatorios intestinales, entre ellos en la EII. Múltiples estudios han demostrado que la CF es un marcador que se correlaciona con la actividad endoscópica y la respuesta clínica terapéutica en la EII[58-60]. También resulta útil en la predicción de la recaída y la recurrencia postquirurgica, habiendo demostrado superioridad sobre otros biomarcadores inflamatorios como PCR, albumina y VSG[59]. Este parámetro presenta como ventajas su obtención por un método no invasivo, el bajo coste asociado a su determinación y que se correlaciona bien con la respuesta clínica y endoscópica al tratamiento. El punto de corte establecido para este parámetro varía entre 50 y 250 µg/g de forma que los valores inferiores a 100 µg/g presentan un alto valor predictivo negativo, es decir, la probabilidad de que exista actividad es muy baja[60]. Cabe señalar, no obstante, que aunque existe un alto grado de evidencia sobre la correlación entre la CF y la actividad endoscópica en la CU y en la EC colónica e ileocolónica[61,62], existe controversia sobre su utilidad como marcador en EC de localización exclusivamente ileal[63].

1.4 Tratamiento farmacológico

Con los tratamientos farmacológicos disponibles en la actualidad no es posible alcanzar la curación total de la EII. El objetivo, por tanto, es controlar y suprimir la actividad inflamatoria, induciendo la curación de la mucosa y tejidos comprometidos, con el fin de lograr la mejoría o desaparición de los síntomas clínicos, mejorar la calidad de vida de los pacientes y evitar las complicaciones a medio-largo plazo. En niños, el tratamiento

además debe orientarse a minimizar la repercusión de la enfermedad en el crecimiento, maduración ósea y estado nutricional, siendo un objetivo fundamental conseguir un crecimiento y desarrollo adecuados, sobre todo en el caso de la EC.

Los tratamientos farmacológicos clásicos se pueden clasificar en tres grupos: fármacos de acción tópica sobre la mucosa intestinal (aminosalicilatos y corticoides orales de efecto local), inmunomoduladores (tiopurinas y metotrexato) e inmunosupresores (ciclosporina y tacrólimus). Más recientemente se han introducido en terapéutica los fármacos biológicos como infliximab, adalimumab, certolizumab, golimumab, natalizumab, vedolizumab y ustekinumab, e inmunosupresores selectivos como los inhibidores de las Janus quinasa (tofacitinib). Estos fármacos habitualmente se reservan como segunda línea de tratamiento en pacientes refractarios o intolerantes a los fármacos clásicos. Sin embargo, una estrategia de tratamiento frecuentemente utilizada en pacientes pediátricos es el *top down* que consiste en iniciar el tratamiento con fármacos biológicos dada la gravedad que habitualmente presenta la EII en este grupo de edad para, posteriormente, desescalar a tratamientos convencionales (aminosalicilatos, nutrición enteral, …)[10,11].

1.4.1 Tratamientos clásicos

Los aminosalicilatos son fármacos que contienen en su estructura la molécula del ácido 5-aminosalicílico (5-ASA o mesalazina), agonista del Receptor Activado por Proliferadores Peroxisomales (PPAR-γ), un factor de transcripción que juega un papel crucial en el mantenimiento de la integridad mucosa intestinal[64]. Principalmente se utilizan en el tratamiento de los pacientes con CU, tanto para la inducción de la remisión como para el mantenimiento de la misma. También han demostrado ser eficaces en la prevención de carcinoma colorrectal en los pacientes con CU o EC de afectación

colónica. Se presentan en comprimidos orales y supositorios, espumas y soluciones (enemas) de aplicación rectal.

Los esteroides son fármacos de primera línea para el control de los brotes moderados-graves en pacientes con EII. Existen dos tipos fundamentales de corticoides empleados en la EII: los sistémicos y los corticoides tópicos de baja biodisponibilidad. Los primeros se administran por vía oral o intravenosa (IV) con el objetivo de inducir remisión ante un brote moderado o grave de EII. Los corticoides tópicos se administran por vía oral o rectal (espuma o enemas) con acción en determinadas localizaciones del intestino y colon. Su gran metabolismo de primer paso hepático impide casi en su totalidad su acceso a la circulación sistémica. Se estima que entre el 10 y el 30% de pacientes con EII son refractarios al tratamiento esteroideo convencional, y que entre el 20 y el 30% desarrollan una enfermedad corticodependiente. Por su toxicidad no deben utilizarse para el tratamiento de mantenimiento.

Los inmunomoduladores clásicos, como las tiopurinas (azatioprina y mercaptopurina) y metotrexato, son fármacos utilizados fundamentalmente para el tratamiento de mantenimiento de la EII, sobre todo en situación de corticodependencia. Las tiopurinas, antimetabolitos de bases purínicas, inhiben la síntesis de purinas *de novo* interfiriendo en la estructura del DNA y, por tanto, en la proliferación celular. La función inmunomoduladora de estos fármacos parece estar relacionada con su capacidad de desencadenar la cascada mitocondrial de la apoptosis de los linfocitos T CD4+, en un proceso que podría estar relacionado con la inhibición de la activación de la proteína Rac1[65]. Por otro lado, metotrexato está indicado en la EC leve a moderada, tanto para inducción de la remisión como en mantenimiento, solo o en combinación con corticosteroides, en pacientes adultos refractarios o intolerantes a tiopurinas y en poblaciones especiales como ancianos. La evidencia disponible en la actualidad no permite una clara recomendación para la utilización de metotrexato en el tratamiento de la CU. Metotrexato ejerce su efecto citotóxico y antiproliferativo mediante la inhibición

de la dihidrofolato-reductasa y la consiguiente síntesis de ácido fólico. No obstante, este efecto no explica por sí mismo su acción antiinflamatoria, que parece estar relacionada con su capacidad de inhibir la síntesis de citoquinas y eicosanoides pro-inflamatorios por mecanismos desconocidos. Otros fármacos con acción inmunomoduladora disponibles en EII son ciclosporina, con evidencia solo en CU, tacrólimus y micofenolato de mofetilo.

Por último, es frecuente la asociación de antibióticos como ciprofloxacino y metronidazol en situaciones especiales como reservoritis, EC perianal, en la prevención de la recurrencia postquirúrgica y ante sospecha de megacolon tóxico y perforación.

1.4.2 Fármacos Biológicos

Los agentes biológicos son anticuerpos monoclonales, inmunoglobulinas principalmente, obtenidos mediante ingeniería genética, capaces de reparar, estimular y mejorar la respuesta inmune del organismo. Estos fármacos permiten detener, controlar o suprimir el avance de la EII modificando el curso de la enfermedad. Además, se ha demostrado que tienen una acción sinérgica con las terapias convencionales.

Los primeros fármacos biológicos con indicación en EII fueron los anticuerpos monoclonales contra el factor de necrosis tumoral alfa (anti-TNF), citoquina central en la cascada inflamatoria y en la respuesta inmune adaptativa. Se administran por vía IV o subcutánea (SC). En la actualidad los fármacos anti-TNF disponibles con indicación en EII son infliximab (IV), adalimumab (SC), golimumab (SC) en CU y certolizumab pegol (SC), sin indicación aprobada en Europa. Están indicados en el tratamiento de la EII activa de moderada a grave que han tenido una respuesta inadecuada al tratamiento con los fármacos clásicos convencionales, incluidos esteroides e inmunomoduladores, o que presentan intolerancia o contraindicaciones a los mismos. Esto incluye el

tratamiento de inducción de la remisión, mantenimiento y prevención de la recurrencia postquirúrgica.

Posteriormente, se han aprobado otros fármacos biológicos con distintos mecanismos de acción, como los inhibidores de integrinas natalizumab (IV, sin indicación aprobada en Europa) y vedolizumab (IV), y los anticuerpos anti-interleucina 12 y 23 (anti-IL12/23) como ustekinumab (IV y SC). Además, recientemente, se ha autorizado el uso de tofacitinib, inmunosupresor selectivo de la Janus quinasa, en CU. Estos fármacos han demostrado en mayor o menor medida su eficacia en la inducción y, especialmente en el mantenimiento de la remisión de la EII, incluyendo a pacientes refractarios o con pérdida de respuesta a anti-TNF.

Fármacos anti-TNF

El uso terapéutico de los fármacos anti-TNF han cambiado drásticamente el manejo de enfermedades inflamatorias crónicas como la EII[66]. Sin embargo, aunque un alto porcentaje de pacientes (70-90%) inicialmente responden al tratamiento, las tasas de pérdida de respuesta después de la inducción son elevadas (20-50%)[1,2,67]. Existen varias razones para esta falta de respuesta. En primer lugar, es necesario mencionar la formación de anticuerpos anti-fármaco (AAF), los cuales se unen al epítopo del fármaco formando inmunocomplejos[68]. Estos inmunocomplejos por un lado bloquean su acción farmacológica y por otro aumentan su eliminación a través del sistema retículo endotelial[69]. El resultado es una disminución de las concentraciones séricas del fármaco y, por lo tanto, una peor respuesta clínica. Se ha estimado que la prevalencia de AAF es del 15-40% para infliximab y del 15-25% para adalimumab[70].

Entre los posibles factores implicados en la falta de respuesta a los fármacos anti-TNF se encuentran también aquellos no relacionados con el sistema inmune, como son un alto índice de masa corporal, hipoalbuminemia o una alta carga inflamatoria, acelerando

todos ellos la eliminación del fármaco[67,71,72]. Por último, los factores farmacodinámicos, como una activación alternativa de la cascada inflamatoria, también pueden ocasionar pérdida de respuesta[67].

En relación a la inmunogenicidad, es ampliamente aceptado que la estructura del anticuerpo monoclonal influye en el desarrollo de AAF[73]. Infliximab es un anticuerpo quimérico formado por una región variable de ratón y una región constante de IgG1 humana mientras que adalimumab y golimumab son anticuerpos IgG1 completamente humanos. Por último, certolizumab pegol es un anticuerpo humanizado conjugado con polietilenglicol. Como la secuencia de aminoácidos de las proteínas de ratón suele ser diferente a la de las proteínas humanas, los anticuerpos de tipo quimérico tienden a ser más inmunogénicos que los anticuerpos completamente humanos.

Otro factor que también influye en el desarrollo de la inmunogenicidad es la vía de administración del fármaco. La vía SC es generalmente más inmunogénica que la IV, principalmente porque la piel es un área que se caracteriza por su capacidad especializada de presentación y procesamiento de antígenos[69,74]. Además, estos fármacos administrados por vía SC experimentan un alto metabolismo en el propio tejido lo que implica una mayor degradación y una menor biodisponibilidad[75].

El desarrollo de AAF, a través de un mecanismo que involucra la activación del complemento y producción de anafilatoxinas, puede ser la causa de la aparición de reacciones infusionales de administración, uno de los principales efectos adversos graves del tratamiento con anti-TNF[76,77]. Por otra parte, el desarrollo de la inmunogenicidad, especialmente si aparecen títulos altos de AAF, está relacionado también con la pérdida de eficacia irreversible del fármaco y con una probabilidad más elevada de desarrollar anticuerpos frente a otro fármaco anti-TNF que para un paciente sin tratamiento biológico previo[78]. Las opciones farmacológicas después del fracaso de estos medicamentos se limitan a vedolizumab, ustekinumab y tofacitinib[79]. Una vez que

todas estas líneas de tratamiento se han agotado, la única alternativa disponible es la cirugía[80,81].

1.5 Farmacocinética de los medicamentos biológicos anti-TNF

La respuesta terapéutica al tratamiento con anti-TNF presenta una alta variabilidad interindividual, probablemente ocasionada por el diferente comportamiento farmacocinético (PK) entre individuos[67]. La tabla 5 muestra los principales parámetros PK de infliximab y adalimumab en pacientes con EII, adaptado de Ordas et al[70].

Tabla 5. Parámetros farmacocinéticos de infliximab y adalimumab

	Infliximab	**Adalimumab**
Vía de administración	Intravenosa	Subcutanea
T_{max}	Dentro de la primera hora	3,2 – 7,8 días
$T_{1/2}$	7,7 - 9,5 días	10 - 20 días
Vd	4,5 – 6,0 L	4,5 – 6,0 L
F	-	64% (variable)

F: Biodisponibilidad; $T_{1/2}$: semivida de eliminación; Tmax: tiempo para alcanzar la concentración máxima; Vd: volumen de distribución.

El comportamiento PK está influenciado por muchos factores, incluidos el sexo, la masa corporal, la vía de administración y la carga inflamatoria sistémica[67,71]. De hecho, biomarcadores elevados de actividad inflamatoria como la PCR y la CF se correlacionan inversamente con la respuesta al tratamiento. Además, en pacientes con altas concentraciones de TNF en suero y mucosa, la pérdida de fármaco en heces a través del colon inflamado podría explicar la necesidad de dosis más altas en la fase de inducción durante las primeras semanas de tratamiento[82]. Finalmente, también se ha sugerido que el aumento de la degradación proteolítica por el sistema reticuloendotelial podría ser un posible mecanismo implicado en el aumento de la eliminación de estos fármacos[69].

Entre los factores que modifican el aclaramiento de estos fármacos cabe mencionar la hipoalbuminemia, habiéndose demostrado que pacientes con bajas concentraciones de albúmina sérica presentan mayor eliminación del fármaco. La hipoalbuminemia conduce probablemente a una mayor exposición para la degradación proteolítica de estos fármacos, debido a la menor expresión del receptor neonatal o de Brambell (FcRn)[71]. Este receptor está implicado en la homeostasis de inmunoglobulinas tanto endógenas como exógenas, ya que las atrapa formando endosomas y las protege de la degradación de las proteasas plasmáticas[83]. Este mecanismo es el responsable de la alta semivida que presentan estos fármacos: 14-21 días. No obstante, como ya comentado, el principal factor que afecta la PK de los anti-TNF es el desarrollo de AAF, que aceleran significativamente el aclaramiento del fármaco y, por tanto, conducen a pérdida de respuesta al tratamiento[71,84,85].

La alta variabilidad inter e intraindividual en la exposición a los anti-TNF hace que la monitorización farmacocinética resulte una herramienta de gran utilidad para la optimización posológica de estos tratamientos. Esta estrategia de control terapéutico permite mantener las concentraciones del fármaco dentro de los márgenes terapéuticos donde la probabilidad de eficacia sea mayor, y la probabilidad de toxicidad y de desarrollo de inmunogenicidad sea mínima. Así, se han propuesto márgenes terapéuticos de referencia para los principales medicamentos biológicos utilizados en el tratamiento de la EII [84,86-90]. Los márgenes terapéuticos para concentraciones mínimas de infliximab y adalimumab, que son los más utilizados, se han fijado en 3-10 µg/mL y 8 -14 µg/mL, respectivamente. De hecho, se ha demostrado que la presencia de concentraciones en la zona superior del margen terapéutico se asocia con una menor inmunogenicidad y con una mayor probabilidad de remisión endoscópica[86,91]. La evidencia disponible para golimumab y certolizumab pegol, no permite caracterizar sus márgenes terapéuticos con fiabilidad.

2. Farmacocinética clínica

La Farmacocinética Clínica es una disciplina de las ciencias de la salud que se ocupa de la aplicación de la PK al cuidado terapéutico seguro y eficaz del paciente individual[92]. Un término considerado muchas veces equivalente a la farmacocinética clínica es la "monitorización terapéutica de fármacos", en terminología anglosajona "Therapeutic Drug Monitoring" (TDM). Ambos comparten el mismo objetivo que es la optimización de los tratamientos, a fin de aumentar la eficacia y seguridad de los mismos. Pero la TDM va más allá, incorporando datos de dosis, efectos y concentraciones del fármaco obtenidas en el mismo paciente, junto con criterios PK y farmacodinámicos (PD). Es decir, la TDM es un sistema de control terapéutico que trata de personalizar la dosificación de los fármacos de acuerdo con el perfil individualizado PK/PD.

Para la implementación de la TDM y la adecuada interpretación de las concentraciones de fármacos, es necesario utilizar modelos farmacocinéticos poblacionales (PopPK). Estos modelos simplifican el complejo sistema biológico del organismo y los procesos que el fármaco experimenta en él, y permiten caracterizar el comportamiento cinético del fármaco en los procesos de absorción, distribución y eliminación, mediante ecuaciones que describen la evolución de sus concentraciones en función del tiempo.

2.1 Farmacocinética poblacional

La farmacocinética poblacional estudia el comportamiento cinético de los fármacos, mediante la estimación de valores medios de los parámetros PK en una población de pacientes, así como la variabilidad inter e intraindividual asociada a dichos parámetros. Esta variabilidad, a su vez, está relacionada con diversos factores como: edad, sexo, peso corporal, factores genéticos, factores ambientales, estados patológicos, situación clínica, etc. Dentro de los métodos utilizados para desarrollar modelos PopPK, el modelo

no lineal de efectos mixtos presenta la ventaja de analizar la influencia de multitud de factores (fisiológicos, patológicos y farmacológicos) sobre los parámetros PopPK[93,94].

El perfil cinético de un fármaco en una población determinada, se puede caracterizar por tres tipos de parámetros poblacionales[95].

- *Parámetros de efectos fijos*. Cuantifican el comportamiento cinético mediante la caracterización de parámetros PK medios y de sus posibles relaciones con factores demográficos, fisiopatológicos y clínicos. Esta información se obtiene tanto en el inicio como durante el curso del tratamiento y refleja el estado fisiopatológico de cada paciente, incluyendo aquellos factores que puedan modificar el perfil cinético del fármaco. Se introducen, por ejemplo, variables como la edad, sexo, peso, altura, naturaleza y gravedad de las patologías, medicación asociada, parámetros bioquímicos, hematológicos, etc.

- *Parámetros de efectos aleatorios interindividuales.* Cuantifican el impacto de la variabilidad PK interindividual, es decir, describen el tipo de dispersión de los parámetros PK en relación a sus valores medios y determinan, mediante las varianzas, la magnitud de la misma. Un ejemplo, para un fármaco X caracterizado con un aclaramiento (CL), viene descrito por la siguiente fórmula:

$$CL_i = CL_T + IIV_i$$

  donde CL_i es el CL de un individuo i, CL_T es el CL medio poblacional (parámetro de efecto fijo). IIV_i es la variabilidad interindividual. Es la desviación del sujeto *i* con respecto a CL_T (parámetro de efecto aleatorio).

- *Parámetros de efectos aleatorios intraindividuales.* Cuantifican el impacto de la variabilidad residual no explicada por el modelo, e incluye la variabilidad cinética

intraindividual, el error analítico, los posibles errores en la especificación del modelo, etc. De acuerdo a esos parámetros individuales determinados, la concentración plasmática a un determinado tiempo observada vendrá determinada por la siguiente fórmula:

$$CP_{i,j} = Y_{i,j} + E_{i,j}$$

donde $CP_{i,j}$ es la concentración observada en un individuo *i*, a un tiempo *j*, $Y_{i,j}$ es la concentración teórica para el individuo *i*, a un tiempo *j*, de acuerdo a sus parámetros PK individuales (combinación de parámetro de efecto fijo + aleatorio) y $E_{i,j}$ es la variabilidad residual.

Para la determinación de los parámetros PopPK, se han desarrollado diferentes estrategias o métodos de análisis, recogidos a continuación:

- *Método de los datos acumulados (Naïve pooled data).* En este método se analizan de manera conjunta todos los datos de concentración-tiempo independientemente de si proceden de un mismo individuo o de varios individuos. El resultado final es la obtención de parámetros PK medios correspondientes a este individuo "único" virtual. No es posible estimar la variabilidad asociada a cada parámetro.

- *Métodos en dos etapas.* En una primera etapa se estiman los parámetros PK para cada individuo mediante el ajuste de un modelo PK a los datos experimentales, por regresión log-lineal o regresión no lineal por mínimos cuadrados. En la segunda etapa se calculan los parámetros PopPK. Si éstos se distribuyen según una distribución normal, se calcula la media y la desviación estándar. Una variación de este método es el "método iterativo" en el cual,

empleando los parámetros PopPK estimados, a partir del método anterior, como información *apriori* del análisis Bayesiano, es posible obtener los parámetros PK de cada uno de los individuos (estimación *posthoc–máximum a posteriori*). Posteriormente, los parámetros PopPK se estiman mediante el cálculo de la media y su desviación estándar. Estos parámetros pueden volver a emplearse como estimas iniciales de una nueva primera etapa para volver a empezar.

- *Método de modelos no lineales de efectos mixtos.* Se basan en modelos farmacoestadísticos complejos que permiten la estimación directa en una sola etapa de los parámetros PopPK y la(s) variabilidad(es). Para ello, utilizan todos los datos disponibles de la población sin necesidad de estimar *a priori* los parámetros individuales. Se emplean técnicas de regresión modificadas: regresión no lineal por mínimos cuadrados expandidos (*extended least squares regression*) o de máxima probabilidad (*máximum likelihood*). Estos algoritmos permiten por un lado identificar y cuantificar los parámetros PopPK medios (efectos fijos) y las constantes que los relacionan con características demográficas, clínicas, genéticas, etc, y por el otro, estimar y cuantificar los efectos aleatorios (variabilidad interindividual y residual).

- *Método de modelos no paramétricos.* A diferencia de los métodos anteriores, no se asume ninguna distribución concreta de los parámetros PK. Representa, en forma de espigas, la función de densidad de las probabilidades discretas estimadas por el método de máxima verosimilitud. La posición de las espigas refleja los valores de los parámetros PK individuales estimados y su altura constituye la probabilidad con la que se han estimado dichos parámetros. Los parámetros en este método forman un conjunto de estimados que hacen difícil su incorporación en los programas informáticos de monitorización cinética habituales.

2.2 Ajuste posológico personalizado

Para poder realizar un ajuste posológico personalizado es necesario conocer los parámetros PK individuales del paciente. En la práctica clínica esta caracterización se realiza ajustando los datos experimentales de concentración-tiempo, disponibles en cada paciente, a las ecuaciones matemáticas dependientes del modelo PopPK para lo que se utilizan distintas técnicas de análisis de datos como la regresión lineal, la regresión no lineal y la estimación bayesiana.

El análisis de regresión lineal consiste en ajustar una serie de datos experimentales a una ecuación de una línea recta con el fin de predecir los valores que tomará la variable dependiente en función de la independiente. Este método ha sido ampliamente utilizado debido a la facilidad para linealizar las ecuaciones farmacocinéticas mediante transformaciones logarítmicas. Sin embargo, en la actualidad se emplean con más frecuencia las técnicas de regresión no lineal, cuya principal diferencia es que no requieren la linealización de la ecuación o transformación de las variables originales. En este caso se utiliza la ecuación correspondiente al modelo sin transformar. En ambas técnicas, el ajuste de los datos se realiza por mínimos cuadrados, cuyo objetivo es minimizar la suma de cuadrados de las diferencias entre los valores de la ecuación del modelo y los correspondientes valores experimentales (concentración-tiempo).

La estimación bayesiana es una técnica alternativa cada vez más utilizada en farmacocinética clínica. La principal diferencia con la regresión lineal y no lineal es que incorpora en el ajuste de los datos no sólo la información experimental obtenida en el individuo, sino también la información conocida *a priori* sobre el comportamiento cinético del fármaco en una población con características demográficas y fisiopatológicas similares a las del individuo (información poblacional)[96]. Los parámetros PopPK necesarios para su aplicación son los comentados previamente (efectos fijos, efectos aleatorios interindividuales y efectos aleatorios intraindividuales). La estimación individualizada de los parámetros PK mediante regresión bayesiana es similar a la

empleada en regresión no lineal por mínimos cuadrados. Los algoritmos bayesianos se basan en parámetros de población obtenidos a partir de métodos paramétricos que asumen una distribución conocida para los parámetros cinéticos del modelo, habitualmente normal o logaritmo normal, de forma que los parámetros PopPK están caracterizados por valores únicos (media, varianza)[97,98]. Las características de estos métodos que han contribuido a su amplia utilización en clínica son las siguientes[99].

- Información experimental mínima. A diferencia de la regresión no lineal, con una muestra es suficiente para poder estimar los parámetros PK individuales.
- Flexibilidad en los tiempos de muestreo. La selección de los tiempos de muestreo es menos crítica debido a la mayor contribución de los parámetros de población en la estimación, especialmente cuando el número de concentraciones obtenidas en el paciente es mínima.
- Versatilidad de modelos PK. Han mostrado su utilidad para todo tipo de modelos complejos.
- Consistencia en los resultados. Evita obtener parámetros muy alejados del margen de variación de los parámetros PopPK, minimizando, entre otros, los riesgos inherentes a la técnica analítica y errores de medicación.

La metodología bayesiana presenta también una serie de limitaciones, como la complejidad de cálculo y la necesidad de utilizar un software específico para ello. Por otro lado, es importante la selección y fiabilidad de los parámetros PopPK utilizados, ya que una inadecuada selección o caracterización de esta información, influye sustancialmente en la fiabilidad y capacidad predictiva de esta metodología, especialmente si la información del individuo es limitada, incorporando el riesgo de tomar decisiones terapéuticas equivocadas.

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II. HIPÓTESIS Y OBJETIVOS

1. Hipótesis del Trabajo

La implantación en la práctica clínica de un programa de monitorización farmacocinética de medicamentos anti-TNF en pacientes diagnosticados de enfermedad inflamatoria intestinal permite aumentar la eficacia terapéutica y disminuir la toxicidad. Las decisiones terapéuticas basadas no sólo en la respuesta clínica y endoscópica sino también en los resultados de la monitorización farmacocinética, permiten mejorar los resultados clínicos a corto y largo plazo en estos pacientes.

2. Objetivo general

Establecer la monitorización farmacocinética de anti-TNF en enfermedad inflamatoria intestinal como herramienta de ayuda en la toma de decisiones y personalización terapéutica en la práctica clínica asistencial.

3. Objetivos específicos

I- Conocer la evidencia científica disponible sobre la monitorización fármacocinética de anti-TNF en enfermedad inflamatoria intestinal y su aplicación en la práctica clínica asistencial para la optimización de tratamientos con estos fármacos.

II- Desarrollar y validar un modelo farmacocinético poblacional de adalimumab que caracterice el comportamiento cinético del fármaco en enfermedad inflamatoria intestinal identificando los factores demográficos, antropométricos, bioquímicos y clínicos con impacto significativo en la farmacocinética.

III- Desarrollar y validar un modelo farmacocinético poblacional de infliximab que caracterice el comportamiento cinético del fármaco en enfermedad inflamatoria intestinal identificando los factores demográficos, antropométricos, bioquímicos y clínicos con impacto significativo en la farmacocinética.

4- Evaluar prospectivamente la eficacia y seguridad a largo plazo de un programa multidisciplinar de monitorización proactiva de infliximab, como herramienta de personalización y optimización terapéutica.

III. TRABAJO EXPERIMENTAL

1. Therapeutic drug monitoring of tumour necrosis factor inhibitors in the management of chronic inflammatory diseases.

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Revista

Annals of Clinical Biochemistry. 2019; 56(1): 28-41.

DOI:10.1177/0004563218782286

Resumen

La terapia con inhibidores del factor de necrosis tumoral (anti-TNF) ha cambiado drásticamente el tratamiento de las enfermedades inflamatorias crónicas. Las principales causas de pérdida de respuesta al tratamiento con estos fármacos son la alta variabilidad individual en la exposición al fármaco, la carga inflamatoria que presenta la enfermedad y la formación de anticuerpos anti-fármaco que aumentan su eliminación.

La monitorización terapéutica (TDM) de estos fármacos aún no está recomendada por todas las sociedades científicas o bien, lo está solamente en pacientes con respuesta inadecuada. La TDM proactiva representa una nueva estrategia con muchos beneficios

clínicos potenciales, incluida la prevención de la inmunogenicidad, reducción de la necesidad de terapia de rescate y una mayor durabilidad del tratamiento con anti-TNF.

La presente revisión se basó en una búsqueda sistemática en la literatura de ensayos clínicos controlados, revisiones sistemáticas, estudios experimentales, documentos de consenso y estudios de cohortes que aborden las mejores prácticas en TDM de anti-TNF.

Aunque la evidencia respalda el uso de la TDM en la práctica clínica para lograr mejores resultados en salud, se han detectado algunas limitaciones como la falta de estandarización de los métodos analíticos para medir las concentraciones de anti-TNF y sus anticuerpos. Otro desafío es el desarrollo de algoritmos proactivos eficaces para identificar los tiempos de muestreo más eficientes y las concentraciones óptimas de estos fármacos. Por último, es necesario establecer el papel que juegan los anticuerpos, especialmente en el manejo y la prevención de la pérdida de respuesta.

La TDM de anti-TNF ofrece un enfoque racional para la optimización de estos tratamientos en las enfermedades inflamatorias crónicas. Aunque los diferentes estudios analizados arrojan poca evidencia concluyente de los beneficios de la TDM proactiva, existe cada vez mayor aceptación de su valor en la práctica clínica.

Review Article

The Association for Clinical Biochemistry & Laboratory Medicine
Better Science, Better Testing, Better Care

Annals of Clinical Biochemistry
2019, Vol. 56(1) 28–41

DOI: 10.1177/0004563218782286
journals.sagepub.com/home/acb
SAGE

Therapeutic drug monitoring of tumour necrosis factor inhibitors in the management of chronic inflammatory diseases

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Abstract

Tumour necrosis factor inhibitor therapy has drastically changed the management of chronic inflammatory diseases. Some important drawbacks that can cause loss of response during treatment with these drugs are related to their large individual variability, the disease burden and the formation of antidrug antibodies that increase its clearance. Therapeutic drug monitoring of these drugs is not yet recommended by all scientific societies, and if so, only in patients with inflammatory symptoms. Proactive therapeutic drug monitoring represents a new strategy with many potential clinical benefits, including the prevention of immunogenicity, a reduction in the need for rescue therapy and greater durability of tumour necrosis factor inhibitor treatment. The review is based on a systematic search of the literature for controlled trials, systematic reviews, experimental studies, guideline papers and cohort studies addressing the best practice in tumour necrosis factor inhibitor therapeutic drug monitoring. Although there is ample evidence supporting the use of therapeutic drug monitoring in clinical practice to achieve better outcomes, some challenges have been detected. Many studies are focused on finding solutions for the lack of standardization of analytical methods to measure tumour necrosis factor inhibitor and antidrug antibodies concentrations. Other challenges are development of effective cost-saving proactive algorithms to identify optimal drug concentrations and the research on the role of antidrug antibodies, especially in the management and prevention of loss of response. Therapeutic drug monitoring of tumour necrosis factor inhibitor offers a rational approach to the optimization of the treatment of chronic inflammatory disease. Although prospective controlled trials yield little conclusive evidence of its benefits, there is growing acceptance of its value in clinical practice.

Keywords

Therapeutic drug monitoring, tumour necrosis factor-alpha inhibitor, antidrug antibody, chronic inflammatory diseases, infliximab, adalimumab, etanercept

Accepted: 21st May 2018

Introduction

The therapeutic use of tumour necrosis factor inhibitors (TNFis) such as infliximab (IFX), adalimumab (AD), etanercept (ETA), golimumab (GOL) and certolizumab pegol (CER), which target tumour necrosis factor-α (TNFα), has dramatically changed the management of chronic inflammatory diseases (CIDs) like

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rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and psoriasis. However, primary non-response or loss of response during treatment may occur in approximately 40% of the patients.[1] There are several reasons for this lack of response. An important drawback of TNFi is the formation of antidrug antibodies (ADAs), which bind to the epitope of the drug and form immune complexes[2] that increase its clearance, resulting in diminished TNFi trough concentrations and inferior clinical outcomes. Furthermore, lack of response can also be caused by non-immune-related factors such as high body mass index or high disease burden, which increases drug clearance. Other pharmacodynamics factors may also lead to non-response.[3]

In relation to the formation of ADA, it is widely accepted that the structures of TNFi influence their immunogenicity.[4] IFX is a mouse/human chimera antibody that joins the variable regions of a mouse antibody to the constant region of human IgG1 whereas ADA and GOL are a fully human IgG1 antibody. Both drugs bind to TNFα and neutralize its activity. On the other hand, ETA is a dimeric fusion protein that joins the human p75 TNF receptor to the fragment crystalline domain of human IgG1 and CER is a humanized Fab′ monoclonal antibody fragment conjugated with polyethylene glycol. Because the amino acid sequence of mouse proteins is usually different from their human counterparts, mouse proteins like those of IFX tend to be more immunogenic than fully human antibodies while dimeric fusion proteins hardly develop immunogenicity.

In clinical practice, dose intensification of TNFi was often the first choice of treatment when loss of response occurred. Other options are adding immunosuppressive co-medication, changing to a different TNFi, changing to a different class of immunosuppressive drug or surgical intervention. There is also evidence that therapeutic drug monitoring (TDM) could be useful in these circumstances. TDM refers to the individualization of dosage by maintaining plasma or blood drug concentrations within a target range.[5] The characteristics of drugs which make TDM useful are a marked pharmacokinetic variability, therapeutic and adverse effects related to drug concentration, a narrow therapeutic index and difficulty of clinical effect measurement. TNFi meet these requirements. In fact, it has been demonstrated that IFX concentrations correlate well with clinical response in patients with IBD and RA[6] and individual treatments can be optimized by dose adjustment based on TNFi trough concentrations and the presence of ADA.

Despite these findings, proactive TDM of TNFi drugs is not yet recommended in the guidelines of all scientific societies. In fact, The National Institute for Health and Care Excellence of United Kingdom,[7] The American Gastroenterological Association[8] and The Gastroenterological Society of Australia[9] consider TDM to be useful mainly in case of lack of response. The purpose of this paper is to provide a literature review of available research evidence on TDM of TNFi.

Analytical methods for measuring TNF inhibitors and antidrug antibodies

There are several techniques for the measurement of TNFi and ADA,[10] such as fluid-phase radioimmunoassay (RIA), solid-phase enzyme-linked immunosorbent assay (ELISA), reporter gene assay (RGA), enzyme immunoassay (EIA) or homogeneous mobility shift assay (HMSA) as is shown in Table 1. However, the lack of a reference standard entails the need to establish cut-off concentrations and therapeutic intervals for each type of assay.

Steenholdt et al.[10] compared four techniques to measure IFX concentrations (RIA, ELISA, RGA and EIA). All tests showed linear correlation ($R^2 = 0.97$ to 0.99) although statistically significant differences between the assays were revealed when different IFX serum concentrations were tested on the same day, on different days and for different individuals. The maximum difference observed for each pair of assays was 1.55 μg/mL for RIA and RGA, 1.41 μg/mL for ELISA and RIA, and 0.48 μg/mL for ELISA and RGA ($P < 0.05$). This study concludes that ELISA, RIA, RGA and EIA are comparable in terms of basic analytical properties, but the lower sensitivity of RGA and the inability of bridging ELISA to detect antidrug antibodies of IgG4 isotype should be considered since they could be of clinical importance.[13] The assumption is that the systematic differences in IFX concentrations and ADAs to infliximab (anti-IFX) that have been observed among the techniques could be due to serum factors and/or matrix effects which affect each of the four assays differently.[10]

Among the available techniques, the most commonly used technique to measure TNFi is ELISA. Schmitz et al.[11] evaluated the analytical performance, agreement and clinically significant differences of three commercially available IFX ELISA kits: Theradiag (Lisa Tracker IFX), Progenika (Promonitor IFX) and apDia (IFX ELISA) using an automated processing system. Although they all have acceptable analytical performance and could thus be used for TDM, the apDia assay had the best precision and agreement to target values. Therefore, it was concluded that the performance of an IFX ELISA should be assessed and cut-off values for TDM should be used with caution.

Table 1. Summary of assays for measuring TNF inhibitor drug and antibody concentration.

Assay	Description[a]	ADA quantification	Observations
Radioimmunoassay (RIA)	Fluid phase: Detecting antibody is labelled with a γ-radiation (^{125}I- TNFα) emitting radioisotope binding to the IgG fractions of the serum sample	ADA cannot be quantified in presence of free TNFi	Cannot distinguish neutralizing and non-neutralizing ADAs Specialized laboratory facilities and trained personnel required
Enzyme-linked immunosorbent assay (ELISA)	Solid phase: Capture ELISA for TNFi and bridging ELISA for ADA. Detection antibody is linked to an enzyme which causes a colour reaction	ADA cannot be quantified in presence of free TNFi.[11,12] IgIG4 ADA isotype cannot be measured[13] (functionally monovalent and therefore cannot 'bridge' in this type of binding assay)	Cannot distinguish neutralizing and non-neutralizing ADAs
Reporter gene assay (RGA)	Direct amount of TNFi activity in a serum sample is quantified using a reporter gene in live cell culture assay	Not affected by detectable free TNFi	Expensive Specialized laboratory facilities and trained personnel required
Enzyme immunoassay (EIA)	Solid phase: Measuring binding of TNFi to patient IgG preabsorbed to protein G and monoclonal antibody to human IgG4 (ADA)	ADA cannot be quantified in presence of free TNFi	Cannot distinguish neutralizing and non-neutralizing ADAs
Homogeneous mobility shift assay (HMSA)	Fluid phase: Fluorescent labelled TNFi or ADA measured using size-exclusion high-performance liquid chromatography	Not affected by detectable free TNFi	Cannot distinguish neutralizing and non-neutralizing ADAs Specialized laboratory facilities and trained personnel required Acid disassociation step prior to detection of ADAs

ADA: antidrug antibodies; TNFi: tumour necrosis factor inhibitor.
[a]All assays can measure infliximab, adalimumab and etanercept as well as their ADAs.[10–13]

An important disadvantage associated to ELISA techniques and other immunoassays is that free IFX could cause a cross-reaction that would prevent optimal detection of anti-IFX.[11] Residual drug concentrations may interfere through competitive inhibition or by forming immune complexes. Studies assessing AD and ADAs to adalimumab (anti-AD) yielded similar findings and the measurement of anti-AD in the presence of (high) drug concentrations is difficult due to drug interference in most assays. In fact, anti-AD is only quantified by ELISA in the absence of detectable amounts of circulating AD.[12] Neither is this technique suitable for measuring anti-AD in complexes with the drug.

To address the issue of false negatives in the detection of ADA, Wang et al.[14] developed a non-radiolabeled HMSA to measure IFX and anti-IFX concentrations in serum samples. Unlike ELISA assays, this test is not subject to free IFX interference, and it includes an acid dissociation step. This procedure makes it possible to separate IFX–anti-IFX immune complexes before conducting the analysis. The technique can also be used to monitor antidrug antibody formation, even in presence of high serum drug concentrations. In relation to AD, the HMSA has also proved effective in overcoming many of the limitations encountered in the solid-phase ELISA and RIA methods,[15] which suggests that it could be useful in TDM.

Llinares-Tello et al.[16] proved as well the usefulness of acid pretreatment for anti-AD detection using Promonitor (ELISA). Although the drug inhibits anti-AD detection by this technique, and progressively higher concentrations of AD cause increasing signal inhibition, the assay showed that this pretreatment led to a significant response increase, particularly at lower free AD concentrations.

The acid pretreatment has also been used before RIA assays. Van Schouwenburg et al.[17] used pH-shift-anti-idiotype antigen binding testing to analyse samples from RA patients. After the dissociation, antibodies were captured using protein A sepharose and anti-ADs were detected using 125I labelled F(ab′)2. This technique allowed the detection of anti-AD in the presence of AD and offered insight on the immune response against AD.

Recent studies focus on more specific ELISA tests. Hock et al.[18] developed a specificity ELISA-based format capable of competitively inhibiting the *in vitro* binding of drug to solid-phase TNF for detecting specifically ADA in patients receiving either AD or IFX; furthermore, Kopylov et al.[19] implemented an alternative sandwich ELISA using antihuman lambda chain antibody for anti-IFX in the detection step which may be less amenable to IFX interference, taking advantage of the exclusively kappa chain composition of IFX.

The development of different analytical techniques with different calibrators allows ADA results to be expressed as arbitrary units towards purified polyclonal mouse antibodies or as a titration value. Gils et al.[20] and Van Stappen et al.[21] each developed a monoclonal antibody to quantify the concentrations of anti-AD and anti-IFX, respectively. This antibody could be used as a calibrator in ADA assays to determine the binding and neutralizing effect of the ADA and contribute to the harmonization of different methods of ADA response analysis. Moreover, these authors suggest that this may also facilitate correlations between the magnitude of ADA response and the clinical outcome of TNFi therapy. However, the main disadvantage of these new calibrators is that the affinity of ADA developed in TNFi-treated patients can be of a different nature to that developed in a mouse.

In view of the difficulty of determining ADAs, some authors have proposed that their persistence should be confirmed through repeated measurements before considering them for therapeutic decisions.

Therapeutic drug monitoring of TNF inhibitors

When TNFis were introduced in clinical practice, routine TDM was not recommended and empiric dosing became the norm. However, deeper understanding of the highly variable pharmacokinetic behaviour of these drugs, combined with growing emphasis on the need for further improvements in clinical outcomes, has led to increasing interest in the role of TDM in treatment optimization.

Although a high percentage of patients (70–90%) initially respond to the treatment, remission rates after induction are still low (20–50%) and, over time, patients are at risk of loss of response to the drug.[5] This inter-individual variability in response is likely to be influenced by the observed inter-individual variability in pharmacokinetics.[5] The pharmacokinetics of TNFi can be due to many factors, including gender, body weight, route of administration and systemic inflammation. In fact, elevated markers of inflammatory activity (C-reactive protein [CRP], fecal calprotectin [FCP], erythrocyte sedimentation rate) have been inversely associated with clinical response. According to Rosen et al.,[22] high serum and mucosal TNF concentrations, and stool IFX loss through the inflamed colon could explain increased drug clearance and, thus, the requirement of higher doses for induction during the first weeks of treatment. Finally, increased proteolytic degradation by the reticuloendothelial system has also been suggested as a possible mechanism that may significantly increase IFX clearance.[22]

On the other hand, it has also been demonstrated that patients with high serum albumin concentrations

show lower IFX clearance and, thus, maintain higher IFX concentrations than patients with lower albumin.[23] However, the main factor that affects the pharmacokinetics and efficacy of TNFi is the development of ADA which accelerates TNFi drug clearance.[5,22–26]

Measurement of drug concentrations and ADA are typically performed only in patients with active inflammatory symptoms or during a potential immune-mediated reaction to TNFi. However, proactive TDM of TNFi concentrations with titration to a therapeutic window represents a new strategy with many potential clinical benefits, including prevention of immunogenicity, less need for rescue therapy and greater durability of TNFi treatment.[27]

TNF inhibitor concentrations

The relationship between TNFi concentrations and clinical outcomes has been reported in the Trough Concentration Adapted Infliximab Treatment trial,[28] which included 483 IBD patients treated with IFX. IFX trough concentrations > 2.79 μg/mL (AUC = 0.681; 95% CI 0.632–0.731) and anti-IFX concentrations < 3.15 μ/mL (AUC = 0.632; 95% CI 0.589–0.676) were associated with a higher remission rate, defined as a CRP of $\leqslant 0.5$ mg/dL. In fact, in anti-IFX-negative samples stratified according to IFX concentration, the median CRP concentration was significantly lower when the serum IFX concentration was $\geqslant 3$ μg/mL compared with < 3 μg/mL (2.0 versus 6.0 mg/L respectively; $p < 0.001$).

In patients with Crohn's disease (CD) and perianal fistulas, higher concentrations to reach a good clinical response could be necessary. In fact, Yarur et al.[29] showed that in this group of patients IFX $\geqslant$ 10.1 μg/mL correlated with higher rates of fistula healing, defined as the absence of drainage, and complete fistula closure and mucosal healing.

The results of the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial,[30] carried out in patients treated with IFX, showed that those with higher concentrations experienced better therapeutic outcomes than those with lower concentrations. Rates of corticosteroid-free clinical remission at week 30 were greater among patients with increased serum IFX trough concentrations. The findings were similar at week 46.

Vaughn et al.[27] conducted a retrospective observational study examining the use of proactive TDM and IFX titration to target concentration in patients with IBD in clinical remission. The main aim was to describe the clinical course of TDM in patients, and the results showed that the probability of remaining on IFX therapy over the study period was greater for patients who achieved trough concentrations > 5 μg/mL (HR:0.03; 95% CI 0.001–0.1; $p < 0.0001$).

Although most studies focus on establishing the lower limits of the target range for trough TNFi concentrations, patients could benefit from dose de-escalation and, therefore, upper limits should also be defined. Vande Casteele et al.[31] proposed TNFi dose de-escalation to reach a target range of 3–7 μg/mL in patients with clinical remission and high IFX trough concentrations. In fact, blind de-escalation of IFX therapy in IBD patients in clinical remission based on symptoms and CRP concentrations has been associated with a high risk of relapse. On the other hand, TDM-based management has been shown to be a more accurate strategy to avoid further relapse of the disease after de-escalation in patients on long-term IFX therapy.[32] It must be borne in mind that, together with the reduction in drug costs, this could also provide additional benefits, considering the potential increased risk of adverse events related to high concentrations. Recently, Van Steenbergen et al.[33] have shown that 65% of patients with IBD who de-escalated to AD 40 mg every three weeks remained in clinical remission for a median of 24 months. In 53% of patients, AD-related adverse events disappeared after dose de-escalation.

Likewise, in patients with RA, the IFX trough serum concentrations determined when inadequate response was detected correlated well with clinical activity. Moreover, a better response was observed in patients with higher trough serum concentrations, and the presence of anti-IFX correlated with disease activity using Disease Activity Score in 28 joints (DAS28) at baseline.[34] Patients treated with detectable concentrations of IFX had a better European League Against Rheumatism Response (EULAR) ($p = 0.002$), DAS28 score ($p = 0.002$) and Simple Disease Activity Index score ($p = 0.001$). On the other hand, Van den Bemt et al.[35] proved that the combination of disease activity, defined as good EULAR response, and IFX serum trough concentrations > 2.5 μg/mL, determined after six weeks of treatment, could be a fair predictor for the early identification of patients who will probably show good response after six months of therapy.

Although most of the studies have been performed using IFX, there is also evidence of the usefulness of TDM in patients treated with AD. A meta-analysis[36] enrolling 14 studies with 1941 patients with IBD shows the presence of anti-AD is associated with a higher risk of loss of clinical response to AD, whereas high AD trough concentrations are associated with greater clinical response rates in patients with CD.

For TNFi in patients with psoriasis, no therapeutic ranges have been established yet. Takahashi et al.[37] reported the association between clinical efficacy and IFX and AD trough concentrations during long-term

treatment. In 32 AD-treated and 20 IFX-treated psoriasis patients, the authors demonstrated that TDM was positively associated with clinical response, and they established >0.92 and >7.84 μg/mL as optimal cut-off values of IFX and AD concentrations, respectively, to achieve $\geqslant$ 75% reduction of the psoriasis area and severity index score (PASI).

Table 2 summarizes the main outcomes obtained in different studies addressing TDM of TNFi and the proposed cut-off or target ranges for serum trough concentrations of IFX, AD and ETA. The selection of studies is based on a systematic search of the literature in PubMed performed up to September 2017 combining various alternative search terms for 'anti-TNF', 'infliximab', 'adalimumab', 'etanercept' and 'drug monitoring'. Studies were included according to the most relevant controlled trials and studies reporting results of clinical outcomes.

Even though some analytical methods have been developed for the measurement of GOL[53,54] and CER[55,56] and their ADAs, more evidence about TDM of these drugs is required to determine its usefulness and no consensus has been reached on a possible therapeutic level or cut-off associated with clinical response, remission or any other outcome.

TNF inhibitor antibodies

Antibodies to TNFis interfere with the binding of the drug to TNF and form immune complexes that hasten drug clearance via the reticuloendothelial system,[57] therefore, placing patients at risk for decreased clinical response.

Although it has been demonstrated that detectable TNFi serum concentrations could reveal circulating ADA,[26,58] it is generally accepted that ADA measurement is not necessary in all patients treated with these drugs. Even so, since a notable percentage of gastroenterology and rheumatology patients (85%) with positive anti-IFX have IFX concentrations $\leqslant$ 1 μg/mL,[59] this determination is currently carried out in the context of undetectable or low IFX concentrations. Under these circumstances, concentrations of anti-AD >4 μg/mL or anti-IFX >9 μg/mL could be used to identify patients who will probably not respond to an increased drug dosage.[48]

The measurement of anti-IFX could also be of interest in the re-induction of IFX therapy after a long period of drug discontinuation in IBD. In this situation (length of discontinuation = 15 months), adequate drug concentrations and absence of anti-IFX early after restarting therapy have been shown to correlate well with both short- and long-term mucosal healing.[60] In fact, the presence of anti-IFX was identified as a negative predictive factor (HR:0.14; 95% CI 0.026–0.74; $p = 0.021$).

Testing for anti-IFX may also warn about the risk of potentially dangerous infusion-related reactions. The development of antibodies to the TNFis may lead to an effect or mechanism involving complement activation and production of anaphylatoxins, which may be the cause of severe side effects.[61,62] In CD patients, the presence of anti-IFX >8 μg/mL has been associated with a relative risk of 2.40 infusion-related reactions[60] (95% CI 1.65–3.66; $p < 0.001$).

In patients with RA treated with IFX, the presence of anti-IFX correlates to disease activity using DAS28 score at baseline.[35] Moreover, in a study carried out by Mazilu et al.,[34] 35 and 10% of the patients had undetectable and subtherapeutic IFX trough concentrations, respectively. Anti-IFX was detected in all of them and none showed EULAR response.

Chen et al.[49] assessed the presence of ADA at months 6 and 12 in 36 AR patients treated with AD and in 34 patients treated with ETA. The presence of anti-ADA was associated with lower EULAR response and lower drug concentrations compared with those without anti-ADA ($p < 0.001$). It is worth noting that, among the TNFi drugs, ETA has the lowest immunogenicity. In this study, none of the patients experiencing inadequate response had ADAs to etanercept (anti-ETA).

Takahashi et al.[37] also showed that the presence of anti-IFX and anti-AD contributes to loss of response to these drugs in patients with psoriasis. In their study, anti-AD and anti-IFX were detected in five out of 32 and in six out of 20 patients with loss of response determined by using PASI75 at weeks 24 and 48, respectively.

Another study based on 77 psoriasis patients receiving biologic therapy also proved that clinical severity scores were significantly higher in the antibody-positive patients.[63] ADAs were identified in the plasma of 25% of the IFX-treated patients and of 29.6% of the AD-treated patients, but in none of the patients in the ETA group. The mean PASI score at the time of blood sampling was significantly lower in ADA-negative patients (1.6 ± 1.6 versus 9.3 ± 11.2 and 2.4 ± 3.5 versus 12.5 ± 8.6 for IFX and AD, in the ADA negative versus ADA positive patients, respectively).

The suggested anti-IFX and anti-AD cut-off concentrations are shown in Table 2. Different approaches for immunogenicity reduction have been proposed. It has been observed that increasing the dose of IFX leads to reduced immunogenicity, suggesting that high drug concentrations might induce tolerance in these patients. However, an alternative explanation for these results could be that, in patients receiving high doses of the

Table 2. Summary of trials associating anti-TNF drug concentration with clinical outcomes.

Authors	Design	Sampling time	Study population	Method	Drug	Cut-off / range (μg/mL)	Clinical outcome	Observations
Vande Casteele et al.[28]	Observational	Maintenance phase	483 CD	RIA	IFX	>2.79	Remission defined as CRP ⩽0.5 mg/dL	ATI concentration of <3.15 μ/mL
Vande Casteele et al.[31]	One-year randomized controlled trial	Maintenance phase	178 CD/ 85 UC	ELISA	IFX	3–7	Remission defined as CRP ⩽0.5 mg/dL	–
Steenholdt et al.[38]	Retrospective	Maintenance phase	69 CD/ 13 UC	RIA	IFX	<0.5	No clinical response	ATI >10 μ/ml
Vaughn et al.[39]	Retrospective observational	Maintenance phase	48 IBD	ELISA	IFX	>5	Probability of remaining on IFX	Proactive TDM
Ungar et al.[40]	Retrospective cross-sectional	Maintenance phase	78 IBD	ELISA	IFX	6–10	Mucosal healing in 80–90%	–
Cornillie et al.[41]	*Post hoc* analysis of ACCENT I[40]	Week 14	385 CD	ELISA	IFX	>3.5	Sustained response	*Post hoc* analysis of ACCENT I[42]
Van den Bemt et al.[35]	Prospective cohort	Week 6	57 RA	RIA	IFX	>2.5	Good EULAR response assessed at month 6	–
St Clair et al.[43]	Multicentre, randomized, double-blind, placebo-controlled trial	Week 54	428 RA	ELISA	IFX	>1	Response of 50% or more	–
Roblin et al.[44]	Prospective observational	Maintenance phase	22 CD/ 18 UC	ELISA	AD	>4.9	Mucosal healing	–
Chiu et al.[45]	*Post hoc* CLASSIC I and II[44,45]	Induction and maintenance	275 CD	ELISA	AD	>5	Predictive of clinical response and remission	*Post hoc* analysis of CLASSIC I/II[46,47]
Ungar et al.[40]	Retrospective cross-sectional	Maintenance phase	67 IBD	ELISA	AD	7–12	Mucosal healing in 80–90%	–
Yanai et al.[48]	Retrospective cohort study	Maintenance phase	142 IBD	ELISA	AD	> 4.5	Failure to respond to dose intensification	
Chen et al.[49]	Prospective	Month 6, 12	36 RA	ELISA	AD	1.274 and 1.046	Good EULAR response assessed at months 6 and 12	–
Pouw et al.[50]	Prospective observational cohort	Maintenance phase	221 RA	ELISA	AD	5–8	Good EULAR response after 28 weeks follow-up	–
Rosas et al.[51]	Prospective	Maintenance phase	57 RA	ELISA	AD	4.3–11.3	DAS28 <3.2	Loss of clinical efficacy of ATA > 3.5 μ/mL
Chen et al.[49]	Prospective	Months 6, 12	34 RA	ELISA	ETA	1.242 and 0.800	Good EULAR response assessed at months 6 and 12	–
Jamnitski et al.[52]	Prospective	Maintenance phase	292 RA	ELISA	ETA	2.1–4.7	Good EULAR response assessed at month 6	–

AD: adalimumab; ATA: antibodies to adalimumab; ATI: antibodies to infliximab; CD: Crohn's disease; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ELISA: solid-phase Enzyme-Linked Immunosorbent Assay; ETA: Etanercept; EULAR: European League Against Rheumatism score; IBD: inflammatory bowel disease; IFX: infliximab; RA: rheumatoid arthritis; RIA: fluid-phase Radioimmunoassay; TDM: therapeutic drug monitoring; UC: ulcerative colitis.

The selection of studies is based on a systematic search of the literature in PubMed performed up to September 2017 combining various alternative search terms for 'anti-TNF', 'infliximab', 'adalimumab', 'etanercept' and 'drug monitoring'. Studies were included according to the most relevant controlled trials and studies reporting results of clinical outcomes.

drug, the presence of residual drug concentrations might interfere with anti-IFX detection.[64]

Another appropriate therapeutic approach to reduce immunogenicity to the TNFi agents and potentiate response to therapy is the use of combination therapies of these drugs with immunosuppressants. There is evidence that IFX concentrations are influenced by the concomitant use of methotrexate (MTX). In fact, the Combination Of Maintenance Methotrexate-Infliximab trial[58] conducted on patients with CD showed that those treated with MTX were less likely to develop anti-IFX than those receiving IFX only (4% versus 20%; $p = 0.01$). The SONIC trial yielded similar results for azathioprine (AZA) in CD patients.[30] In this study, anti-IFX were detected at week 30 in one out of the 116 patients (0.9%) receiving combination therapy and in 15 out of the 103 patients (14.6%) treated only with IFX.

On the other hand, co-treatment with immunomodulators in patients restarting after a prolonged period of drug discontinuation with low IFX concentrations has been identified as a positive predictive factor of mucosal healing (HR: 6.0; 95% CI 1.3–27; $p = 0.019$).[60] In view of this fact, and of the increased risk of developing severe infusion-related reactions after re-initiation (19.5% of the patients),[60] concomitant immunosuppressant therapy should always be considered in IFX retreatment cases.[60,62]

This strategy also seems to be useful in RA patients treated with AD. In fact, in a prospective observational cohort study including 221 RA patients,[50] median AD concentrations were higher in those taking MTX concomitantly than in those on monotherapy, 7.4 μg/mL (95% CI 5.3–10.6; $p < 0.001$) and 4.1 μg/mL (95% CI 1.3–7.7; $p < 0.001$), respectively. Similar results were obtained with ETA.[65] In a study carried out with 274 RA patients, those receiving combined treatment with MTX achieved clinical remission, evaluated by DAS28 index and radiographic non-progression (effect difference 22.05%, 95% CI 13.96–30.15; $p < 0.0001$).

Practical issues in therapeutic drug monitoring

In most of the studies, TNFi concentrations were determined after the loading dose and before an administration (trough concentration), once the steady state had been reached. However, there is little evidence regarding the best time for TDM. Clinical algorithms using TDM monitoring have been proposed as a tool in the management of loss of response to TNFi drugs[28,37,51] to facilitate decision-making.

TDM could also be useful at the beginning of the TNFi treatment. In fact, most patients who develop anti-IFX do so within the first 12 months of IFX therapy.[66] This strategy is also supported by the findings that IFX trough concentrations at day 14 were lower in patients with acute severe UC compared to moderately severe UC, possibly due to a higher inflammatory burden and/or increased drug clearance[67] which therefore increases the probability of occurrence of anti-IFX. Furthermore, Vermeire et al.[68] showed that four weeks after starting treatment, patients with lower IFX concentrations were at increased risk for developing high titre of anti-IFX (>8 μ/mL), during the follow-up. Moreover, IFX concentrations below 4 μg/mL at week 4 had a positive predictive value of 81% to detect the ensuing development of high titre of anti-IFX.

The usefulness of the initial TDM was also demonstrated in a *post hoc* analysis[41] of the randomized controlled trial to assess the benefit of maintenance infliximab therapy in patients with active CD who respond to a single infusion of infliximab (ACCENT I study).[42] Cornillie et al.[41] proposed to carry out IFX TDM after 14 weeks in order to detect the need for early dose escalation, especially in patients with CD. In this group, trough IFX concentrations $\geqslant 3.5$ μg/mL and decrease CRP concentrations $\geqslant 60\%$ at week 14 have been associated with better response at follow-up week 54 (OR: 3.5; 95% CI 1.1–11.4) and (OR: 7.3; 95% CI 1.4–36.7), respectively.

On the other hand, there is no clear evidence in the literature concerning the development of proactive TDM algorithms to individualize therapy in patients in clinical remission.[69] After the initial dose optimization, continued concentration-based dosing has not been proved to be superior to clinically based dosing for maintaining remission after one year in patients with CD or UC. In fact, Vande Casteele et al.[31] found that the percentage of patients who achieved remission with clinically based and with concentration-based dosing was similar: 66 and 69% ($p = 0.686$), respectively. However, continued concentration-based dosing was associated with fewer flares during treatment. Moreover, in a retrospective analysis of 264 patients with IBD receiving IFX maintenance therapy,[70] drug titration to a target concentration (proactive monitoring) was associated with better clinical outcomes, including greater drug durability, less need for surgery and/or hospitalization, and lower risk of ADAs than TDM after patient loss of response (reactive monitoring).

A rather controversial issue is that of discontinuation of TNFi therapy in cases of deep remission. Papamichael and Vermeire[71] showed that after stopping TNFi treatment because of sustained remission under combination therapy with immunosuppressant, 85% of the patients had to restart treatment again. Retreatment is usually well tolerated and the success rate is high, but attention should be paid to the fact that patients have an increased risk of developing

infusion reactions and delayed hypersensitivity during IFX reintroduction. Some authors have proposed the discontinuation of IFX or AD in IBD only in patients in remission with undetectable drug concentrations. Ben-Horin et al.[72] conducted a retrospective cohort study examining the duration of relapse-free survival after TNFi cessation, finding that relapse occurred in 16/20 (80%) of the patients who stopped TNFi while having measurable drug concentrations, against 9/28 (32%) of the patients with undetectable drug concentrations (OR: 8.4; 95% CI 2.2–32; $p = 0.002$). Moreover, the duration of relapse-free survival was significantly longer in patients with absence of the drug compared to those with detectable drug concentrations ($p < 0.001$, log-rank test). These authors suggested that the finding of an undetectable TNFi drug level in a patient with stable, long-term, deep remission may identify a subset of patients whose clinical remission is no longer dependent on TNFi treatment.

Another controversial issue is the suitability of switching between different TNFi drugs in the event of loss of response. Although it is common clinical practice, several studies have shown that patients who develop anti-IFX are more likely to develop anti-AD in comparison with TNFi naïve patients (33% versus 18%; $p = 0.039$).[73] Moreover, in this study, response to AD was limited even in switchers with no anti-IFX. On the other hand, patients with an immunogenic response against a first TNFi drug (IFX or AD) had a better clinical response to ETA compared to patients without ADA.[74] These findings raise the question of whether a second TNFi treatment should be offered to patients with RA when, in the absence of ADA, an initial treatment with a TNFi fails. In these patients with therapeutic drug concentrations and no clinical response, probably, it is not worth trying other TNFi because the lack of efficacy is associated with the mechanism of action. Therefore, a drug addressed to other therapeutic target should be selected.

Analogous results have been found in IBD patients treated with TNFi when they were switched to another therapy.[75] Yanai et al.[48] carried out a retrospective study in a cohort of 247 patients, demonstrating that patients with IFX trough concentrations above 3.8 μg/mL or AD trough concentrations above 4.5 μg/mL showed no clinical response to dose escalation or switch to another TNFi with 90% specificity. On the other hand, these groups of patients responded better to symptomatic therapy or to non-TNFi treatments (immunomodulators and/or different biological agents).

Finally, although postmarketing global safety experience with biosimilar IFX is continuously growing and ensures that switching is both safe and well tolerated, some physicians still advise caution when switching from an innovator IFX. There are still few studies comparing drug concentrations and effectiveness before and after the switch. A study carried out by Smits et al.[76] demonstrated that switching from innovator IFX to CT-P13 (biosimilar IFX) in a real-life cohort of 83 IBD patients did not have a significant impact on short-term clinical outcomes. Median IFX trough concentrations increased from 3.5 μg/mL (range 0–18) μg/mL to 4.2 μg/mL (range 0–21) μg/mL at week 16 ($p = 0.010$) with no significant changes in the medians of CRP and FCP concentrations during follow-up. Similar results have been obtained in the NOR-SWITCH trial,[77] a study where switching from originator IFX to biosimilar CT-P13 was compared with maintained treatment with originator IFX in IBD patients. Jørgensen et al.[77] demonstrated that switching from innovator to CT-P13 was not inferior to continued treatment with innovator IFX. Changes in CRP: (−0.07; 95% CI −0.17, 0.04) and (−0.04; 95% CI −0.18, 0.10) and FCP: (−0.08; 95% CI −0.27, 0.10) and (0.21; 95% CI −0.03, 0.44) in CD and UC, respectively. Comparable results were also seen for trough serum concentrations and presence of TNFi.

Cost-effectiveness of therapeutic drug monitoring

The use of biological drugs in many CID has led to a great improvement in clinical results, but it is also associated with an important impact on health care costs, driven mainly by medication costs. TDM is increasingly used to optimize TNFi therapy to improve its efficacy and security, but it could also be justified based on economic reasons. Actually, several studies suggest that the cost-effectiveness of TDM-based strategies is higher than that of empirical dose management.

One controlled trial[3] included 69 CD patients with secondary IFX failure. They were randomized to receive empirical dose intensification or TDM-based dose adjustment. At week 12, the clinical response was similar in both groups. However, in the intention-to-treat analysis, costs proved significantly lower (€3,140) in the TDM group, mainly due to discontinuation of ineffective treatments.

The study carried on by Vande Casteele et al.[31] included 263 CD or UC treated with IFX and with stable responses. During the optimization phase, doses had been adjusted to reach trough concentrations between 3 and 7 μg/mL. After this period, they were randomized to being subjected to a clinically based strategy or to a TDM-based strategy. Although one year after the optimization phase the percentage of patients who achieved clinical and biochemical remission was similar, the TDM group proved significantly

cost saving (28%). This strategy was more cost effective as a result of dose reductions in patients with trough concentrations > 7 μg/mL.

There are currently no randomized controlled trials comparing both strategies in RA patients treated with AD or IFX. Nevertheless, two modelling approaches, both of them based on the Markov chain model, included this population[78,79] and concluded that TDM was cost saving. Nonetheless, it should be noted that the use of this kind of modelling could yield biased results.

Despite the difficulties to extrapolate the results of these studies to other health care systems, given the high costs of TNFi drugs and the comparative lower costs associated to its determination, the use of TDM as a cost-effective strategy in clinical practice is gaining acceptance.

On the other hand, a recent review of clinical effectiveness and cost-effectiveness of TDM of TNFi using different ELISA kits versus standard care for CD carried out by the National Institute for Health Research[80] concludes that testing is not cost effective for IFX. However, the authors emphasize that the results should be viewed cautiously in view of the limited evidence. In addition, they recommend clinicians to be mindful of variation in performance of different assays and of the absence of standardized approaches to patient assessment and treatment algorithms.

Discussion

There is currently ample evidence supporting the use of TDM as a tool for therapy optimization in IBD, RA and psoriasis patients with the purpose of achieving better outcomes at lower costs. However, not all scientific societies recommend its use. In fact, scientific societies[7–9] only recommend TDM in two scenarios: patients whose disease loses response to treatment and may need a higher dose of TNFi to try to recover clinical response, and patients whose disease responds to treatment with TNFi and may continue at the same level of treatment.

The implementation of TDM of TNFi is one of the great challenges in everyday clinical practice, largely due to the lack of standardization of analytical methods for the measurement of TNFi and ADA concentrations.[10,20,21] ELISA is the most widespread analytical technique,[11,18] despite the significant disadvantages it entails. Free TNFi concentrations could cause a cross-reaction that would prevent optimal detection of ADA,[11,12,18] which is why it only quantifies the antibodies in the absence of detectable amounts of circulating drug. In order to avoid these false negative problems, Wang et al.,[14] Llinares-Tello et al.[16] and Van Schouwenburg et al.[17] developed an acid pretreatment to allow the separation of TNFi–ADA immune complexes before conducting the analysis. Another handicap associated with ELISA is the inability to detect IgG4 anti-IFX, which could constitute up to 89% of IgG anti-IFX in patients treated with IFX over prolonged periods of time.[12,13]

The relationship between the IFX concentrations and clinical outcomes in IBD patients has been reported in several studies.[27–29,38,39] Some authors go even further, recommending a target range of 3–7 μg/mL and proposing TNFi dose de-escalation in patients with clinical remission and high IFX trough concentrations.[31] Similar conclusions have been obtained from studies that included RA patients, and a target $> 2.5\,\mu$g/mL has been proposed for this population.[35]

Although different studies have been carried out in patients with IBD, RA and psoriasis treated with AD[37,43,44,46,51] and rheumatologic patients treated with ETA[47,50] establishing a therapeutic efficacy window, there is weaker evidence relative to the usefulness of TDM of these drugs.

The measurement of ADA in daily clinical practice is only considered in the context of undetectable or low drug concentrations,[48,49] since their presence has been associated with disease activity.[28,38,51] In this scenario, concomitant use of an immunosuppressant (MTX or AZA) enables immunogenicity reduction and may be a useful strategy to increase TNFi concentrations.[30,58,69,81]

Although early optimization of IFX during or immediately after the induction phase seems to improve clinical remission rates, especially in CD patients,[41,68] most of the accepted algorithms based on TNFi and ADA trough level measurements have been developed for loss of response management.[28,53] There is evidence for determining drug concentrations at week 14[41,81] and during the maintenance phase.[27,39,53] However, in patients with symptoms suggestive of lack of response, TDM of IFX and anti-IFX would be advisable during the induction phase[41,67] (two or four weeks after its first administration).

Figure 1 shows our strategy proposal for comprehensive patient management during the entire treatment with TNFi drugs. In addition, a new algorithm for TDM-guided proactive decision-making that includes early optimization in patients treated with IFX is proposed in Figure 2.

Future challenges should include refinement of the optimal concentration range in each patient and the ideal moment for TDM. Although knowledge of mechanisms that regulate TNFi distribution and clearance is still limited, population PK/PD modeling[24] will contribute to the definition of underlying covariates that

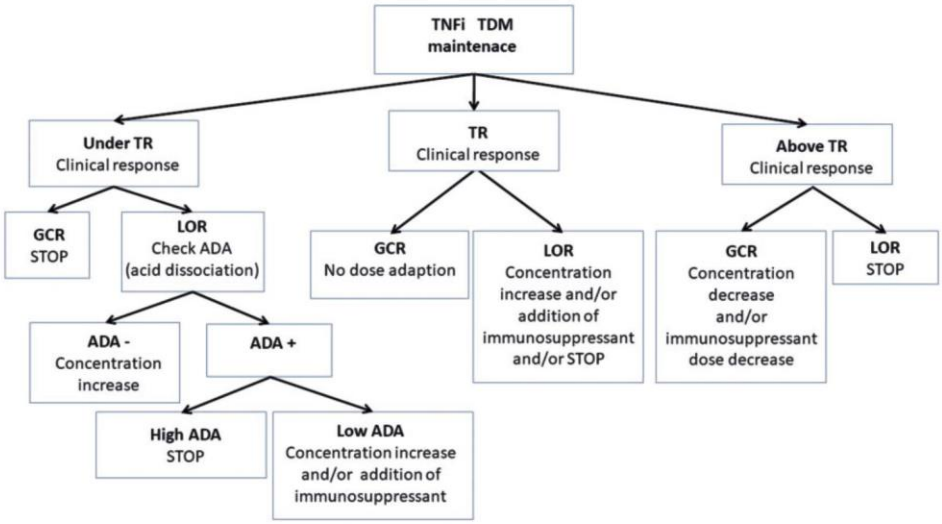

Figure 1. Algorithm for TDM-guided decision-making over the treatment with TNF inhibitors in patients with CIDs. ADA: antidrug antibodies; GCR: good clinical response; LOR: loss of clinical response; TDM: therapeutic drug monitoring; TNFi: tumour necrosis factor inhibitor; TR: therapeutic range.

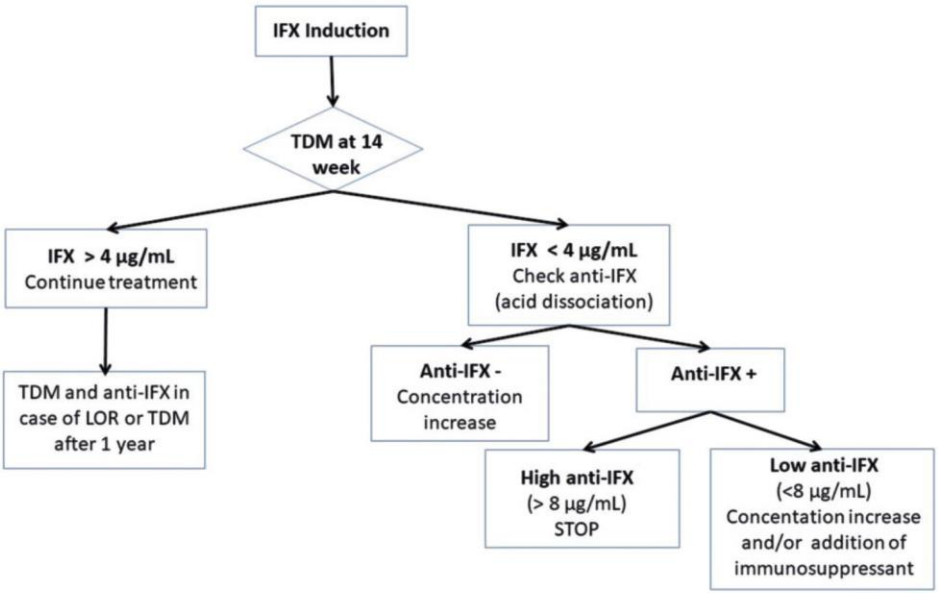

Figure 2. Algorithm for TDM-guided decision-making for early optimization of infliximab treatment in patients with CIDs. Anti-IFX: antidrug antibodies to infliximab; IFX: infliximab; LOR: loss of clinical response; TDM: therapeutic drug monitoring.

may explain the observed intersubject and interoccasion variability in drug concentrations.

Conclusions

TDM of TNFi offers a rational approach to the optimization of IBD, RA and psoriasis therapies. There is increasing evidence that drug concentrations correlate with clinical outcomes, and therapeutic algorithms integrating clinical response with TDM have been developed. Although there is little evidence from prospective controlled trials to definitively demonstrate the benefits of TDM, its value in clinical practice is gaining increasing acceptance.

Acknowledgements

This article was prepared at the invitation of the Clinical Sciences Reviews Committee of the Association for Clinical Biochemistry and Laboratory Medicine.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval was not required because this work is a review of biomedical literature.

Guarantor

JGS-H.

Contributorship

JGS-H, NR and MVC conceived and designed the study. JGS-H, NR and FM selected studies and researched literature. JGS-H, NR, MVC and AM-S wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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2. Biomarkers of disease activity and other factors as predictors of adalimumab pharmacokinetics in inflammatory bowel disease

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Revista

European Journal of Pharmaceutical Sciences. 2020; 150: 105369.

DOI :10.1016/j.ejps.2020.105369

Resumen

Adalimumab es un fármaco con indicación en el tratamiento de la enfermedad inflamatoria intestinal. El objetivo del estudio fue desarrollar un modelo farmacocinético poblacional de adalimumab en estos pacientes, evaluando los posibles biomarcadores de actividad de la enfermedad y otros factores, y sus implicaciones en la dosificación del fármaco.

Se realizó un estudio prospectivo observacional en el que se incluyeron pacientes adultos diagnosticados de enfermedad de Crohn y colitis ulcerosa en tratamiento con adalimumab bajo un programa de monitorización proactiva de las concentraciones sdel

fármaco. Las concentraciones séricas de adalimumab se determinaron principalmente antes de la administración por enzimoinmunoensayo (ELISA). Se desarrolló un modelo farmacocinético poblacional basado en 303 datos de concentraciones de 104 pacientes utilizando metodología de modelado de efectos mixtos no lineales. Como grupo de validación externo se seleccionaron al azar 20 pacientes adicionales con sus respectivas 65 concentraciones del fármaco

Se ha desarrollado un modelo monocompartimental con absorción y eliminación de primer orden que describe adecuadamente la evolución temporal de las concentraciones del fármaco. El índice de masa corporal, la calprotectina fecal, la disminución inexplicada de las concentraciones y el dispositivo de administración mostraron una influencia significativa en el aclaramiento aparente del fármaco (valor p <0,001).

La calprotectina fecal fue el biomarcador de actividad inflamatoria que mostró el impacto más relevante en la exposición a adalimumab, superior a la proteína C reactiva y la albúmina, lo que demuestra que podría ser útil para el ajuste de la dosis del fármaco

El modelo farmacocinético poblacional desarrollado caracteriza adecuadamente la exposición a adalimumab en pacientes con enfermedad inflamatoria intestinal.

European Journal of Pharmaceutical Sciences 150 (2020) 105369

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Biomarkers of disease activity and other factors as predictors of adalimumab pharmacokinetics in inflammatory bowel disease

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ARTICLE INFO

Keywords:
Adalimumab
Inflammatory bowel disease
Pharmacokinetics
Faecal calprotectin
Body mass index
Population pharmacokinetic model

ABSTRACT

Inflammatory bowel disease (IBD) is commonly treated with adalimumab. The main objective of the study was to develop a population pharmacokinetic model of adalimumab in IBD patients evaluating the potential biomarkers of disease activity and other factors and its implications in adalimumab dosing.

A prospective observational study was performed in adult patients diagnosed with Crohn's disease and ulcerative colitis treated with adalimumab and following a proactive therapeutic drug monitoring of serum concentrations. Adalimumab serum concentrations (ASC) were quantified mainly prior the administration using an enzyme-linked immunosorbent assay (ELISA). A population pharmacokinetic model was developed based on 303 ASC data of 104 IBD patients using non-linear mixed effect modelling approach. Sixty-five ASC from 20 additional patients were randomly selected as an external validation group.

A one-compartment model with first order absorption and elimination best describe the ASC time course. Body mass index (BMI), faecal calprotectin (FCP), unexplained decline in ASC and the specific administration pen device exhibited significant influence on apparent clearance (p-value < 0.001).

FCP was the inflammatory activity biomarker showing the most relevant impact on adalimumab exposure, higher than C-reactive protein and albumin, and may be useful for adalimumab dosing adjustment.

The population-based pharmacokinetic model developed adequately characterized adalimumab exposure in IBD patients. The unexplained decline in ASC, FCP, BMI and the specific administration pen device were identified as meaningful variables significantly influencing adalimumab pharmacokinetics.

1. Introduction

Adalimumab is a recombinant fully human immunoglobulin (IgG1) anti-tumour necrosis factor α (TNF-α) that inhibits the binding of TNF-α to its receptors. This drug has dramatically changed the management of chronic inflammatory diseases such as ulcerative colitis (UC), Crohn's disease (CD), rheumatoid arthritis, psoriatic arthritis and plaque psoriasis, among others (FDA, 2019; EMA, 2019).

The relationship between adalimumab serum concentrations (ASC) and clinical outcomes has been highlighted in several studies (Sanchez-Hernandez et al., 2019). In patients diagnosed with inflammatory bowel disease (IBD), trough adalimumab serum concentrations (TASC) at steady state above 5 mg/L (Mitrev et al., 2017) were associated with increased clinical response. Accordingly, a therapeutic range of 5–12 mg/L was proposed for this drug. However, TASC above 8 mg/L were reported to be necessary to reach not only clinical response but also endoscopic remission (Juncadella et al., 2018). Consequently an updated therapeutic range of 8–12 mg/L has been proposed in the clinical practice.

The pharmacokinetics (PK) of adalimumab in CD patients has been commonly characterized using population PK modelling (PopPK) (Berends et al., 2018; Sharma et al., 2015; Ternant et al., 2015; Vande Casteele et al., 2019). However, the potential influence of the main inflammation biomarkers currently taking into account to assess adalimumab treatment response on adalimumab PK has not been evaluated.

Adalimumab exhibits considerable inter- and intra-patient PK variability, which has been associated with treatment failure over time

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https://doi.org/10.1016/j.ejps.2020.105369
Received 21 January 2020; Received in revised form 4 April 2020; Accepted 28 April 2020
Available online 19 May 2020

and/or with the need for dose escalation. Many factors have been identified as sources of this variability, including gender, body weight, hypoalbuminemia, genetics, systemic inflammation and the formation of anti-drug antibodies (ADA) (Vande Casteele and Gils, 2015). Improving knowledge of the PK behaviour of adalimumab together with potential factors related to exposure and therapeutic response may be useful to improve the safety and efficacy of treatment with this drug.

After subcutaneous administration of 40 mg of adalimumab every other week, absorption and distribution were slow and variable, the peak of serum concentrations being reached 5 days after administration (FDA, 2019; EMA, 2019). The elimination half-life of adalimumab was estimated at two weeks. Its bioavailability appeared variable and was estimated to be approximately 64%. This variability in drug disposition could be among the reasons for the high percentage of IBD patients (20–50%) failing to respond satisfactorily to standard adalimumab dosages (González-Fernández et al., 2019; Vande Casteele and Gils, 2015).

The aim of the study was to develop a PopPK model of adalimumab in patients diagnosed with IBD assessing factors with potential clinical relevance.

2. Material and methods

2.1. Study design

This was a prospective observational study performed in adult patients undergoing treatment with adalimumab and following a proactive therapeutic drug monitoring (TDM) program ran between the Gastroenterology Service and the Pharmacokinetics Laboratory of the Hospital Pharmacy Service. The study was conducted at the University Hospital of Salamanca (Spain) between September 2015 and December 2019.

2.2. Subjects and data collection

Serum samples were collected from adult patients diagnosed with moderate or severe CD or UC treated with adalimumab. The inclusion criteria were: Partial Mayo Clinic Score (IMp) > 4 for UC (Lewis et al., 2008) and Harvey-Bradshaw Index Score (HB) > 7 and/or Simplified Endoscopic Activity Score for Crohn´s Disease (SES-CD) > 4 for CD (Daperno et al., 2004; Harvey and Bradshaw, 1980).

The Pharmacy Service provided Humira® solution for subcutaneous injection in two different pre-filled pen devices according to the prescribed dose: 40 mg and 80 mg pen devices. The use of pen devices was explained to patients. The initial dose of adalimumab was selected according to the recommendations provided in the drug data sheet (FDA, 2019; EMA, 2019): 160 mg at week 0 followed by 80 mg at week 2. Afterwards, adalimumab dose adjustment was performed according to TDM. Patient adherence was assessed by checking the medication dispensing records and ratified with a personal care interview with the patient. Non-adherent patients were excluded from the study.

The following information were recorded for each patient: age, gender, height, total body weight (TBW), ideal body weight (IBW), ideal adjusted body weight (IABW), body surface area (BSA), body mass index (BMI), type of disease, extent of the disease, CD behaviour, age at diagnosis, age at start of adalimumab, perianal fistulising disease, concomitant use of immunomodulatory drugs (i.e. thiopurines or methotrexate), extraintestinal manifestations (musculoskeletal, dermatologic, hepatopancreatobiliary or ocular), serum albumin, faecal calprotectin (FCP), C-reactive protein (CRP), type of administration pen device and previous anti-TNF treatments. Disease extent and behaviour were defined according to the Montreal classification (Gomollon et al., 2017). BMI was calculated as: weight (kg)/height^2 (m). IBW was calculated as: 50.0 + 0.9 * (height (cm) – 152) in men and 45.5 + 0.9 * (height (cm) – 152) in women (Chennavasin and Brater, 1982). IABW was calculated as: IBW + 0.4 * (TBW - IBW) (Bauer, 2001). BSA was calculated as: weight (kg)$^{0.425}$ * height (cm)$^{0.725}$ * 0.007184 (Du Bois and Du Bois, 1989). Sampling time and dosing regimen available at the time of the ASC extraction were also recorded.

The selected patients were randomly assigned to either the PopPK development group (80% of patients) or the external validation group (20% of the patients).

2.3. Laboratory tests

Adalimumab serum concentrations and ADA were determined using an enzyme-linked immunosorbent assay (ELISA) developed by Sanquin Laboratories, Amsterdam, the Netherlands. In this technique, serum adalimumab binds to TNF and is detected by an anti-F(ab')2-adalimumab, enzyme horseradish peroxidase labelled antibody. The disadvantages of this assay are: it is a drug sensitive test, since it is not able to reliably detect ADA bound to the drug (when ASC > 0.5 mg/L) and the inability of bridging ELISA to detect antidrug antibodies of IgG4 isotype since these antibodies could be of clinical importance (Aalberse et al., 2009). Therefore, this assay presents a high rate of false negative ADA. Antibodies were measured in patients with ASC < 1 mg/L (Barlow et al., 2016). For these reasons, unexplained decline in ASC (UDASC) was defined as a decrease of at least 33% in ASC during the maintenance phase with no apparent cause (confirmed adherence to treatment, no modification of adalimumab dosage and no significant increase in inflammatory markers or scores (FCP, PCR, albumin, IMp, HB, SES-CD)) and reversible with dose intensification. The lower limit of quantification (LLOQ) of this assay was 0.06 mg/L. ADA were defined as positive when titers were > 12 AU/mL according to laboratory assay. ASC values below the LLOQ were excluded from the formal analysis (Xu et al., 2011).

2.4. Therapeutic drug monitoring and samples

At the beginning of the study, all the patients who were already under chronic treatment with adalimumab were monitored. Patients who started treatment were monitored for the first time at week 4. TDM was repeated after two months in patients for whom dose adjustment had been recommended. Proactive TDM was routinely performed every six months once the TASC were within therapeutic range (8–12 mg/L). For patients with TASC below the therapeutic range, a dose escalation (interval decrease and/or dose increase) was proposed. On the other hand, an interval increase was proposed for patients with supra-therapeutic TASC.

Serum adalimumab concentrations were obtained mainly in the 24 h prior to adalimumab administration. However, in patients with inflammatory signs and symptoms, mostly when low TASC were suspected, additional samples were taken during the drug administration interval in order to determine the optimal therapeutic decision.

2.5. Population pharmacokinetic analysis

Non-linear mixed effects modelling using the first-order conditional estimation method with INTERACTION (FOCEI) was used to develop the PopPK model using NONMEM® version 7.3.0 (Icon Development Solutions, Ellicott City, MD, USA (Beal et al., 2009)). Data visualization and statistical analyses, including evaluation and representation of model and simulation outputs were carried out in R version 3.3.1 (Comprehensive R Network, http://cran.r-project.org).

Adalimumab PK was initially described using a linear one-compartment disposition model. The PopPK model was parameterized in terms of apparent volume of distribution (V/F), apparent clearance (CL/F) and first order absorption rate (Ka). Interindividual variability (IIV) of PK parameters was assumed to follow a log-normal distribution and, consequently, an exponential model was used (Eq. (1)).

$$P_i = P_{pop} \times e^{\eta_i} \quad (1)$$

Where P_i is the PK parameter estimate for the individual i, P_{pop} is the typical value (population median) of the PK parameter and η_i is the inter-individual random effect. η values were assumed to be independently and identically distributed with a mean of 0 and a variance of ω^2: $\eta \sim N(0, \omega^2)$.

Residual unexplained variability (RUV) was modelled using a proportional error model (Eq. (2).).

$$C_{ij} = \hat{C}_{ij} \times (1 + \varepsilon_{1ij}) \quad (2)$$

Where C_{ij} is the jth measured serum concentration in individual i, $\hat{C}_{ij}$ is the model predicted jth value in individual i, and ε_{ij} is the residual random error for measurement j in individual i. ε_{1ij} is the proportional component of the residual random error. ε values were assumed to be independently and identically distributed with a mean of 0 and variance of σ^2: $\varepsilon \sim N(0, \sigma^2)$.

The magnitude of IIV and RUV was expressed approximately as a coefficient of variation (CV,%). Correlation between random parameters and inter-occasion variability (IOV) were graphically explored and evaluated if any trend was observed.

All the previously described variables in Section 2.2. (demographic, clinical, therapeutic, etc.) were considered for the initial covariate analysis. A covariate screening based on physiologically meaningful, visual graphical inspection and stepwise linear regression of the relationships between the IIV of adalimumab PK parameters and the continuous covariates and analysis of variance (ANOVA) for the categorical covariates was performed. Only physiological plausible covariates and sufficiently represented in the studied population that were statistically significant ($p < 0.05$) and had a coefficient of determination $r^2 > 0.10$ with an IIV parameter were considered to be of potential clinical relevance and were further evaluated one by one in the PK model following a stepwise covariate model-building methodology with NONMEM. Additionally, covariates more sensitive to time-varying processes, such as development of immunogenicity, pen device administration or comedications, were also evaluated with NONMEM. For each model, improvement in data fit was assessed using the likelihood ratio test (forward p-value < 0.05; backward p-value < 0.01), the reduction in IIV and RUV, and the precision and bias of PK parameter estimates (Savic and Karlsson, 2009).

2.6. Model evaluation

The PopPK model developed was assessed using goodness-of-fit plots, considering scatterplots of observed versus population predicted concentrations and versus individual predicted concentrations as well as prediction corrected visual predictive check (pcVPC) (Bergstrand et al., 2011; Ette and Williams, 2007; Nguyen et al., 2017). Goodness-of-fit plots were performed for both the development and the validation datasets. The pcVPC was carried out for the development group as internal evaluation. In the pcVPC, the 5th, 50th and 95th percentiles of the observed ASC were presented, as well as the 5th, 50th and 95th percentiles together with the 95% confidence interval (CI) for the corresponding model-based predicted percentiles computed for each bin across time since first dose and replicates. Additionally, for the external validation group, a prediction corrected numerical predictive check (pcNPC) of the ASC obtained at day 7 and day 14 after dose was performed. A total of 1000 replicates of the original dataset were generated for pcVPC and pcNPC analysis.

The accuracy of parameter estimates and robustness of the final PopPK model were assessed using 1000 bootstrap replicates constructed by random sampling from the original dataset. Model parameters were estimated for each bootstrap replicate and the resulting values of the models that converged successfully were used to estimate the median and 95% confidence interval (CI) from the individual replicates.

2.7. Model-based simulations

Deterministic simulations of adalimumab concentration-time profiles were carried out with the final PopPK model to investigate the impact of the factors identified on the expected adalimumab exposure and/or response to adalimumab as well as its potential clinical relevance. A sufficient number of adalimumab administrations was simulated to reach steady state in the different simulated scenarios, based on the variables identified in the final model.

2.8. Ethical considerations

The study was approved by the Biomedical Ethics Committee of the Health Area of Salamanca after evaluating compliance with ethical standards and good clinical practice.

3. Results

3.1. Patient characteristics

A total of 129 patients were included in the study and 389 ASC were determined. Five patients were excluded due to lack of adherence. On the other hand, 21 ASC (5.4%) below LLOQ were discarded with detection of ADA for 19 of them. One-hundred and four patients (303 ASC) were selected for the development of the adalimumab PopPK model and 20 patients were selected for its external validation (65 ASC). No positive ADA were measured in these patients.

The clinical and demographic baseline characteristics of the patients selected for the development of the adalimumab PopPK model in this study, stratified by development and validation group, are shown in Table 1. Table 2 shows the TDM outcomes in both groups.

3.2. Population pharmacokinetic model

Adalimumab PK was best described by a one-compartment model with first order absorption and elimination. Adalimumab absorption rate was fixed at 0.0062 1/h as previously reported by Ternant et al. (2015).

Based on previous adalimumab PK models, corporal size metrics were *a priori* evaluated on the CL/F of the drug. Among the anthropometric parameters evaluated (TBW, IBW, IABW, BMI and BSA), BMI with a power relationship yielded the highest degree of influence on adalimumab elimination and was considered the base model for the following covariates assessment. Interindividual variability of V/F could not be estimated due to the sparse sampling typically carried out in TDM.

In the covariate analysis conducted, the variables UDASC, FCP and administration pen device (40 mg or 80 mg) exhibited significant influence on CL/F (p-value < 0.001) and were incorporated into the final model. The inclusion of these variables in the model reduced IIV on CL/F and RUV by 21% and 10%, respectively. Adalimumab CL/F in the final model is described in Eq. (3).

$$CL/F = 0.0157 \times (BMI/23.7)^{1.11} \times (1 + 1.20 \times UDASC) \times (1 + 0.24 \times PEN) \times (FCP/74)^{0.064} \quad (3)$$

Where adalimumab CL/F, BMI and FCP are apparent clearance, body mass index and faecal calprotectin, expressed in L/h, kg/m^2 and mg/kg, respectively; UDASC and PEN are binary covariates where 0 represents no unexplained decline in TSAC and 40 mg pen device, and 1 represents UDASC and 80 mg pen device, respectively. The pen device seemed to have no effect on patients with BMI < 20 kg/m^2 based on graphical exploration. Diagnosis (CD or UC) did not exhibit significant influence on CL/F (p-value = 0.257).

Table 1
Baseline characteristics of patients selected for the development and validation of the adalimumab PopPK model.

		Development group	Validation group
N		104	20
Gender [male (%)]		58 (55.8)	13 (65.0)
Age at diagnosis [median in years (IQR)]		36 (29–53)	33 (29–46)
Age at start of adalimumab [median in years (IQR)]		43 (32–56)	36 (29–48)
Body weight [median in kg (IQR)]		68 (56–80)	73 (65–82)
Body mass index [median in kg/ m^2 (IQR)]		23.7 (21.1 – 27.1)	23.5 (22.5 – 26.3)
Body surface area [median in m^2 (IQR)]		1.8 (1.6 - 2.0)	1.9 (1.8 - 2.0)
Lean body weight [median in kg (IQR)]		60.0 (51.2 - 67.3)	63.2 (58.7 – 70.7)
IBD type	CD [n (%)]	84 (79.8)	15 (75.0)
	UC [n (%)]	20 (19.2)	5 (25.0)
CD Location	L1 (ileal) [n (%)]	29 (34.5)	8 (53.3)
	L2 (colonic) [n (%)]	13 (15.5)	1 (6.7)
	L3 (ileocolonic) [n (%)]	42 (50.0)	6 (40.0)
	L4 (upper GI disease) [n (%)]	2 (2.4)	0 (0.0)
CD Behaviour	B1 (nonstricturing, nonpenetrating) [n (%)]	40 (47.6)	7 (43.7)
	B2 (stricturing) [n (%)]	27 (32.2)	5 (31.3)
	B3 (penetrating) [n (%)]	17 (20.2)	4 (25.0)
Perianal disease [n (%)]		17 (16.3)	5 (25.0)
UC Extent	E1 (proctitis) [n (%)]	5 (25.0)	1 (20.0)
	E2 (left-side colitis) [n (%)]	3 (15.0)	1 (20.0)
	E3 (pancolitis) [n (%)]	12 (60.0)	3 (60.0)
Extraintestinal manifestations [n (%)]		37 (35.6)	6 (30.0)
Concomitant IMM [n (%)]		47 (45.2)	8 (40.0)
	Thiopurines (azathioprine, 6-MP) [n (%)]	39 (37.5)	7 (35.0)
	Methotrexate [n (%)]	8 (7.7)	1 (5.0)
Previously anti-TNF treatment		34 (32.7)	4 (25.0)
Patients with dose adjustment based on TDM [n (%)]		57 (54.8)	14 (70.0)

CD: Crohn's disease; IBD: inflammatory bowel disease; IMM: immunosuppressants; IQR: interquartile range; UC: ulcerative colitis; TNF: tumour necrosis factor; 6-MP: mercaptopurine; TDM: therapeutic drug monitoring.

Table 2
Therapeutic drug monitoring outcomes of patients included in the development an validation group.

	Development group	Validation group
Serum samples (n)	303	65
Adalimumab serum concentrations [average in mg/L (SD)]	9.8 (4.3)	9.1 (4.8)
Unexplained decline in adalimumab serum concentrations [n (%)]	9 (3.0)	4 (6.2)
Treatment		
Induction (n,%)	48 (15.8)	7 (10.8)
Maintenance (n,%)	255 (84.2)	58 (89.2)
Administration pen device		
40 mg (%)	275 (90.8)	60 (92.3)
80 mg (%)	28 (9.2)	5 (7.7)
Faecal calprotectine [median in mg/kg (IQR)]	74 (17 - 282)	54 (15–217)
C-reactive protein [median in mg/dL (IQR)]	0.15 (0.04 – 0.39)	0.25 (0.10 – 0.62)
Serum albumin [median in g/dL (IQR)]	4.5 (4.3 – 4.7)	4.5 (4.2 – 4.8)

IQR: interquartile range; SD: standard deviation.

3.3. Internal and external validation

Adalimumab PK parameters were estimated with a correct precision (residual standard error ≤ 35% in all cases) and lack of systematic bias (shrinkage ≤ 20% for all parameters). In addition, the magnitudes of the IIV on CL/F and RUV were consistent with previous information (Berends et al., 2018; Vande Casteele et al., 2019). A sensitivity analysis imputing the LLOQ value (0.06 mg/L) to the LLOQ observations and ADA measured in the development group (n = 13) showed the consistency of the final parameter estimates (differences < 20%, data not shown). No significant differences were observed between the median PK parameters obtained from the bootstrap analysis and the final PK parameter estimates (table 3). Moreover, estimated PK parameters were within the 95%CI of parameters obtained in the bootstrap. In addition, only 9 runs out of 1000 were skipped due to near boundary estimates,

Table 3
Adalimumab population pharmacokinetic parameters.

Parameters	Final Model Estimate	RSE (%)	Shrinkage	Bootstrap (n = 1000*) Mean	95% CI
CL/F (L/h)	0.0157	3		0.0158	0.0152 - 0.0166
BMI-CL/F	1.11	16		1.11	0.81 – 1.42
UDASC-CL/F	1.20	28		1.25	0.54 – 1.86
FCP-CL/F	0.0644	24		0.0645	0.0388 – 0.0900
Pen-CL/F	0.239	35		0.253	0.088 – 0.389
V/F (L)	11.2	9		11.3	9.5 – 13.0
Ka (1/h)	0.0062 (fix)			0.0062 (fix)	
IIVCL/F (CV,%)	23.2	9	14	22.7	19.3 – 26.5
RUV (CV,%)	21.7	13	12	21.4	19.2 – 23.9

$CL/F_i = CL/F^*(BMI/23.7)^{BMI\text{-}CL/F} * (1 + UDASC\text{-}CL/F) * (1 + Pen\text{-}CL/F) * (FCP/74)^{FCP\text{-}CL/F}$.

If no UDASC, UDASC-CL/F = 0.

If 40 mg pen device or BMI < 20 kg/m^2, Pen-CL/F = 0.

* 9 runs over were skipped cause of nearly boundary.

BMI: body mass index (mg/m^2); CI: confidence interval; CL/F: apparent clearance; CV: coefficient of variation; FCP: faecal calprotectin; IIVCL/F: interindividual variability on clearance; Ka: absorption rate constant; Pen: adalimumab pen device; RSE: residual standard error; RUV: residual unexplained variability; UDASC: unexplained decline in adalimumab serum concentrations; V/F: apparent volume of distribution.

proving the stability and robustness of the final model.

Goodness-of-fit plots showed adequate descriptive capacity and absence of pronounced bias in both groups, development and external validation (Fig. 1).

Adalimumab serum concentrations and variability were adequately described throughout the assessment of the follow-up treatment in the development population group using the final PopPK model, as shown in Fig. 2. Although concentrations values and shape of the profile are not directly interpretable from the pcVPC, since a correction is applied,

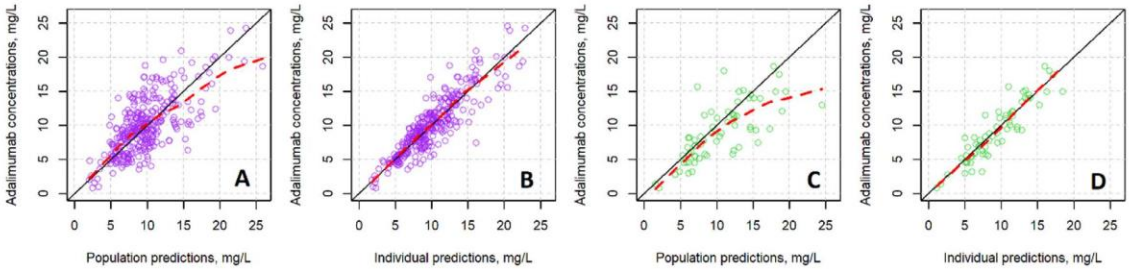

Fig. 1. Goodness-of-fit plot of adalimumab concentrations with the final model for development (A-B) and validation populations (C-D); black solid line, identity line; open circles, adalimumab serum concentrations observed; blue dashed lines, locally weighted scatterplot smoothing (LOWESS).

this methodology is useful an extensively applied for model evaluation with heterogeneous dosage administrations. The pcVPC (Fig. 2) shows the adequate performance and predictions of the adalimumab PopPK model developed. The pcNPC shows a proper prediction performance of the model at day 7 and 14 after adalimumab last dose for the external evaluation group, thus supporting the adequate prediction capacity of the model (supplementary 1).

4. Discussion

Ulcerative Colitis and CD are the most common forms of IBD. These pathologies share many similarities in terms of symptoms, risk factors and treatment, the main difference being the area of the digestive system where inflammation occurs: in UC only the mucosa of the large intestine or the colonic mucosa is affected, whereas in CD, transmural lesions can occur in any part of the digestive tract (Gomollon et al., 2017).

In recent years, adalimumab has contributed to markedly improve the prognosis of IBD (Annese et al., 2016). According to its data sheet (FDA, 2019; EMA, 2019), the dosage of adalimumab is 40 mg every other week via subcutaneous injection, which may be increased to 40 mg every week or 80 mg every other week in cases the recommended dose fails to achieve desired response. PK variability is currently highlighted as a key source of differences (Vande Casteele et al., 2015) in treatment response to adalimumab, supporting that higher drug concentrations are associated with sustained response (Juncadella et al., 2018; Roblin et al., 2014). In addition, the development of immunogenicity associated with this type of drugs is well known and associated with low drug concentrations (Paul et al., 2014). Therefore, improving the understanding of adalimumab PK behaviour is essential to address its therapeutic management and reduce the immunogenicity developed in patients under treatment.

This study aimed at developing a PopPK model of adalimumab in IBD patients based on real-world data obtained from patients under short and long-term treatment. ASC were properly described following a one-compartment open model with first order absorption and elimination. Adalimumab CL/F was demonstrated to be significantly affected by BMI, FCP, the specific drug administration device and the UDASC. No significant differences in adalimumab elimination were found regarding diagnosis (UC or CD), in agreement with previous studies (Ordás et al., 2012; Vande Casteele and Gils, 2015).

The results obtained in this study indicated that a higher CL/F was seen for patients with higher BMI. Therefore, in order to reach target TASC between 8 and 12 mg/L, patients with higher BMI are more likely to require higher doses than those established in the drug data sheet. Several previous studies described TBW as the best anthropometric parameter to describe adalimumab elimination (Sharma et al., 2015; Vande Casteele et al., 2019). By contrast, BMI was the best body size metric affecting adalimumab CL/F in our study population. This difference could be explained by the higher BMI in the development population of the current analysis (23.7 kg/m^2) compared to the BMI of the previous study (Vande Casteele et al., 2019) carried out in adult population (22.6 kg/m^2).

Immunoglobulin drugs administered subcutaneously undergo a high presystemic metabolism (Ordás et al., 2012; Richter et al., 2012 and Wang et al., 2008). Moreover, adipose tissue is a metabolically and immunologically active tissue (Grant and Dixit, 2015). Therefore it can be assumed that patients with increased adipose tissue may experience

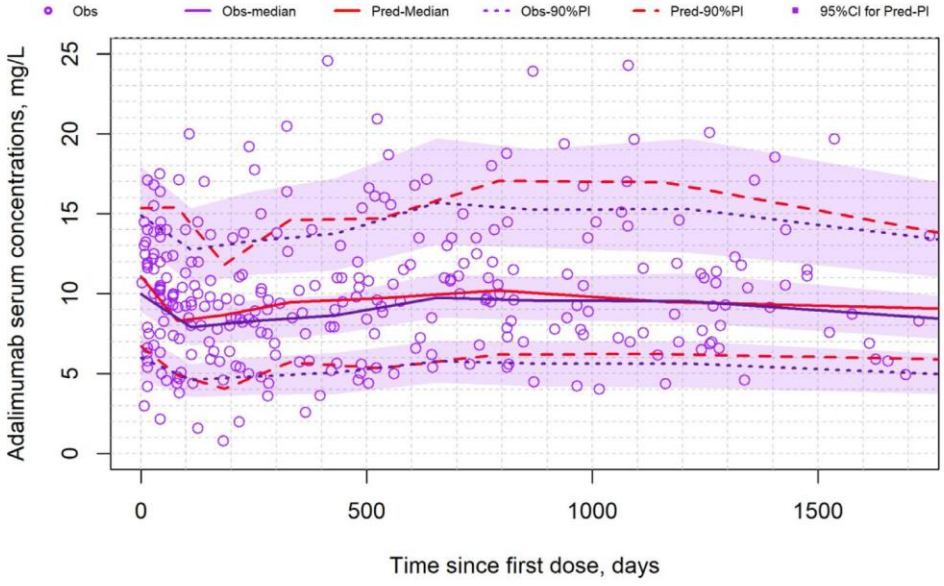

Fig. 2. Prediction-corrected visual predictive check (pcVPC) for the concentration-time after-dose profiles of adalimumab in the development population (internal evaluation). Purple open circles, adalimumab observations (Obs); purple solid line, median of the Obs; red solid line, median of the predicted adalimumab concentrations (Pred); purple dashed lines, 5th and 95th percentile of the Pred (90% prediction interval, PI); red dashed lines, 5th and 95th percentiles of the Obs; purple-shaded area, 95% confidence interval (CI) for the 5th, 50th and 95th percentiles of the Pred.

higher degradation of the drug due to increased of inflammatory mechanisms and consequent catabolism via reticuloendothelial system (Hodkinson, 2017). Therefore, bioavailability could be potentially decreased leading to lower drug concentrations. These findings are supported by previous studies where therapeutic response to adalimumab in IBD patients was lower in patients with higher BMI (Bond et al., 2016; Bultman et al., 2012). Similar results were obtained for patients using adalimumab for the treatment of conditions other than IBD (Højgaard et al., 2016). It should be noted that the effect of BMI on adalimumab PK would be most likely on bioavailability rather than on CL/F. However, bioavailability of adalimumab could not be estimated due to the absence of intravenous drug administration data.

Moreover, the results presented in this work showed a significant influence of the specific administration pen device on adalimumab exposure. Using the 80 mg pen could decrease the ASC reached compared to two administrations with the 40 mg pen device, probably due to a non-linear bioavailability with dose. This could be explained by the previously mentioned metabolism after subcutaneous administration. The deterministic simulations showed the different drug exposures after using 40 mg and 80 mg pen devices of adalimumab when the equivalent intensification dosing of 40 mg weekly and 80 mg each other week were administered accounting for three body size compositions (Fig. 3). According to these results, obese patients (IMC > 30 kg/m^2) could not reach endoscopic remission therapeutic concentrations using the 80 mg pen each other week and dose intensification of 40 mg weekly was proposed for these patients. However, the low percentage of patients treated with the adalimumab 80 mg pen in the presented work (9.2%) justifies the need for additional studies to support these findings.

The influence of the inflammatory burden on the increase of adalimumab CL/F has been previously reported by Vande-Casteele et al. (2015). Among the inflammatory activity biomarkers analysed in our study, FCP and CRP showed a positive influence on adalimumab CL/F, while serum albumin showed a negative influence. Among all these inflammatory variables, FCP had the greatest impact on adalimumab CL/F decreasing its IIV by 16%. One of the novelties regarding previously published adalimumab PopPK models is the assessment of this new biomarker that has been recently introduced in clinical practice. In previous studies, CRP and albumin were the most influential inflammatory markers of adalimumab elimination (Sharma et al., 2015; Vande Casteele et al., 2019). However, the inclusion of FCP in the PK model as a disease activity biomarker seems to provide a better explanation of adalimumab clearance IIV than CRP.

Multiple studies have shown that FCP is a reliable marker of endoscopic activity and therapeutic response as well as a good predictor of relapse and post-operative recurrence in UC (Lin et al., 2014; Mumolo et al., 2018). To this end, the FCP is considered superior to CRP and other faecal biomarkers (Mosli et al., 2015). Thus, FCP is a non-invasive, cost-effective and safe parameter not only helpful in predicting adalimumab exposure but also in related to adalimumab treatment response and mucosal healing in UC.

Recent studies have also shown good correlation between FCP and the endoscopic activity of colonic and ileocolonic CD evaluated by various endoscopic index, such as the Crohn's Disease Endoscopic Index of Severity (CDEIS) and SES-CD (Lin et al., 2014; Lobatón et al., 2013). This correlation is higher than the ones presented by clinical activity index and CRP (Kawashima et al., 2017; Mosli et al., 2015).

On the other hand, there is controversy regarding the influence of the location of CD on the accuracy of the FCP to predict endoscopic lesions. While in some studies the accuracy is similar in different locations (Arai et al., 2016; Jensen et al., 2011), in most cases the correlation between FCP and endoscopic activity is lower in ileal disease than in colic or ileocolic (Lobatón et al., 2013; Stawczyk-Eder et al., 2015). Some authors have questioned the validity of these findings since the exploration of the ileum was performed by ileocolonoscopy and was considered incomplete since visualizing proximal small intestine sections was not possible (Guardiola et al., 2018). Recently, several studies addressing this issue have been conducted through a complete study of the ileum (Arai et al., 2016; Cerillo et al., 2015;

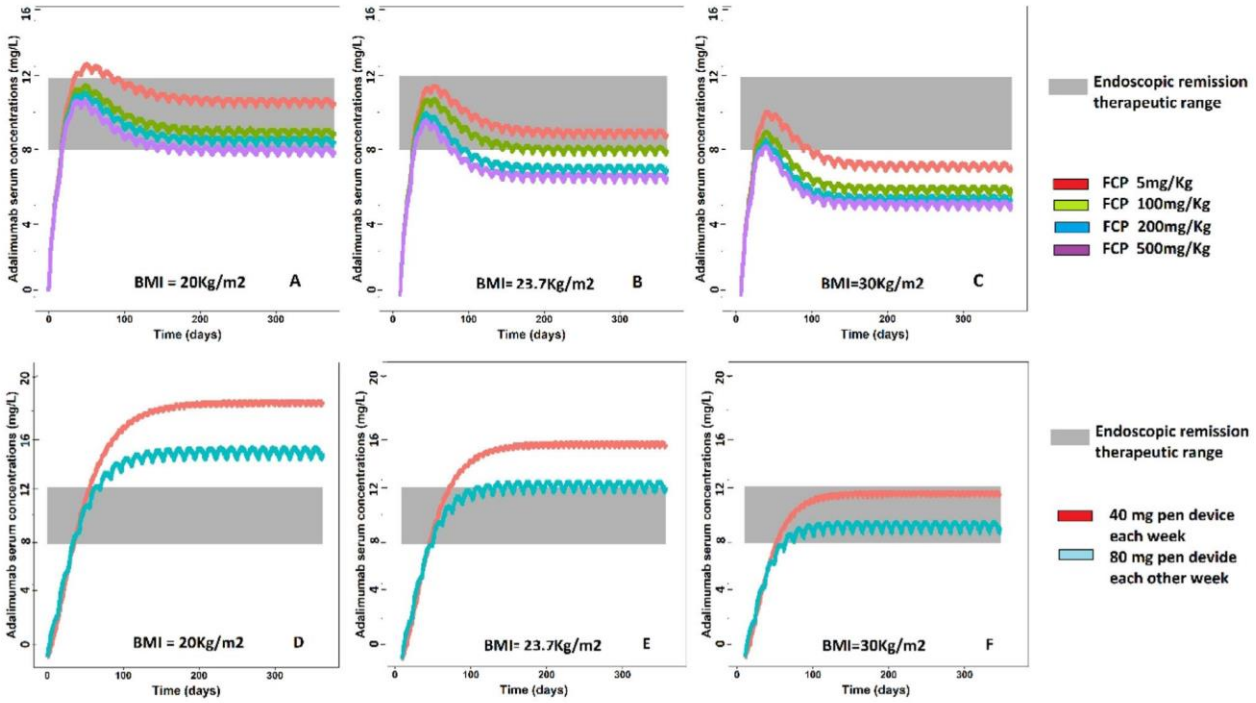

Fig. 3. Adalimumab serum concentrations simulated depending on the faecal calprotectin (FCP) of the patient for body mass index (BMI) of 20 kg/m^2 (A), 23.7 kg/m^2 (median of study population) (B) and 30 kg/m^2(C) when the standard doses of 160 mg (week 0), 80 mg (week 2) and 40 mg each other week is administrated with the 40 mg pen device. On the lower panels adalimumab serum concentrations simulated of equivalent intensification doses of 40 mg weekly and 80 mg each other week for patients with BMI of 20 kg/m^2 (D), 23.7 kg/m^2 (E) and 30 kg/m^2 (F), respectively, with a median FCP of 74 mg/Kg (median of study population) are shown.

Kawashima et al., 2017). All of them suggested that FCP was a reliable marker of ileal endoscopic activity, although less relevant than in colic disease. In the adalimumab PopPK model presented in this research, FCP was the best disease biomarker in patients with ileal CD. Adalimumab PK behaviour in patients with CD located in the small intestine can be characterized by FCP better than CRP or albumin although its impact on the disease activity is not yet well established. The total number of patients (29) with disease exclusively ileal CD was small and did not allow definitive conclusions.

Model-based simulations yielded lower ASC than expected for patients with high FCP. For example, an average patient (BMI = 23.7 kg/m^2) treated with a standard adalimumab dosage would not reach TASC within the therapeutic range for endoscopic remission (TASC > 8 mg/L) with high FCP ≥ 200 mg/kg. These results are consistent with the relationship between TASCs observed at steady state and FCP values in the development group (supplementary). In the raw data, a slight increase in the proportion of patients not reaching the therapeutic range for endoscopic remission (TASCs > 8 mg/L) with increasing FCP values was observed. In addition, obese patients (BMI ≥ 30 kg/m^2) could not reach therapeutic concentrations (TASCs ≤ 8 mg/L) whatever FCP values considered. Therefore, FCP has been identified as a relevant factor to predict adalimumab exposure in absence of the development of immunogenicity and it can be a powerful biomarker for adalimumab dosage individualization in patients with high detectable FCP levels before the onset of clinical symptomatology.

One of the biggest challenges of TDM of anti-TNF and the use of PopPK models is the correct interpretation of the analytical assay used (Gorovits et al., 2018; Sánchez-Hernandez et al., 2019) to measure ADA. Among the available techniques, the most commonly used is ELISA. Most of the commercial ELISA analytical methods to determine ADA are drug-sensitive tests, since they are unable to detect ADA bound to the drug. Thus, ADA can only be measured in the absence of detectable ASC and therefore, the proportion of ADAs and the quantitative effect of them on CL/F could be underestimated. A drug-sensitive test was used in PopPK models developed by Ternant et al. (2015) and Sharma et al. (2015). In addition, Berends et al. (2018) could only measure ADA when ASC was below 5 mg/L. On the other hand, Vande Casteele et al. (2019) developed an in-house ELISA assay applied for accurate quantification of ADA with concentrations up to 25 mg/L. However, different reports (Van Stappen et al., 2018 and Papamichael et al., 2019a) conclude that drug-tolerant assays did not offer clinical benefits over drug-sensitive assays.Taking into account the mentioned limitations of drug-sensitive ELISA, the PopPK presented in this work, can be a very helpful tool to identify the development of immunogenicity prior to the presence of detectable ADA, when a proactive monitoring strategy is applied in the clinical setting and specially since UDASC are mainly related to start of immunogenicity (Bloem et al., 2015). Therefore, model-based assessment of ADA presence could improve the efficacy and persistence of adalimumab treatment (Papamichael et al., 2019b; Sanchez-Hernandez et al., 2020).

One of the strengths of our study is the development of an adalimumab PopPK model with an adequate descriptive and predictive performance including variables that are typically available during the follow-up of IBD patients, supporting its extrapolation to clinical practice. In addition, special emphasis should be placed on the identification of new factors that affect adalimumab exposure such as BMI and FCP, and can be used for optimizing individual drug dosage regimens.

Due to the lack of information in the absorption and distribution phases, the PopPK model developed was focused on characterizeing the elimination of the drug, which can limit the accurate estimation of drug exposure. However, the purpose of this study was not to characterize the drug's whole time-concentration profile, but to establish a model with an adequate description capacity of adalimumab PK and exposure that would be easy to implement in clinical practice as a guiding tool for dosage decision-making. Moreover, adalimumab data reliability was limited by the lack of homogeneity, since the only serum samples collected at protocoled sampling times were coming from patients who started adalimumab treatment after the beginning of the study.

5. Conclusions

In conclusion, the population-based pharmacokinetic model developed adequately characterized adalimumab PK in IBD patients after subcutaneous administration. The UDASC, BMI and FCP have been identified as meaningful variables with significant influence on adalimumab clearance and exposure. The PopPK model presented could be a useful tool both for immunogenicity development detection and for adalimumab dosage individualization, possibly leading to an improvement in adalimumab treatment efficacy and safety. Future prospective studies are required to support the findings obtained.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

JG Sánchez-Hernández and F Muñoz have served as speakers for Abbvie Spain.

Acknowledgments

The authors want to thank the support received from all the staff of our Pharmacokinetics Laboratory, Pharmacy and Gastroenterology Services.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2020.105369.

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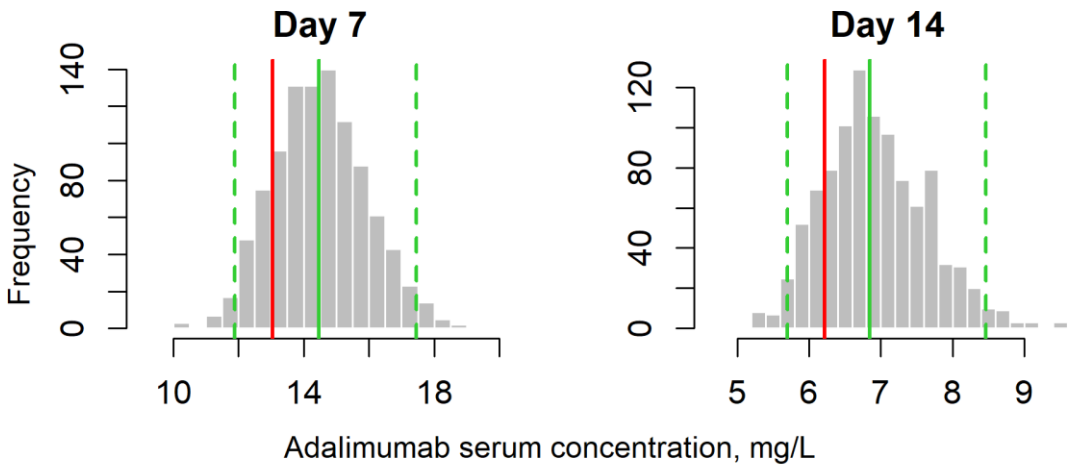
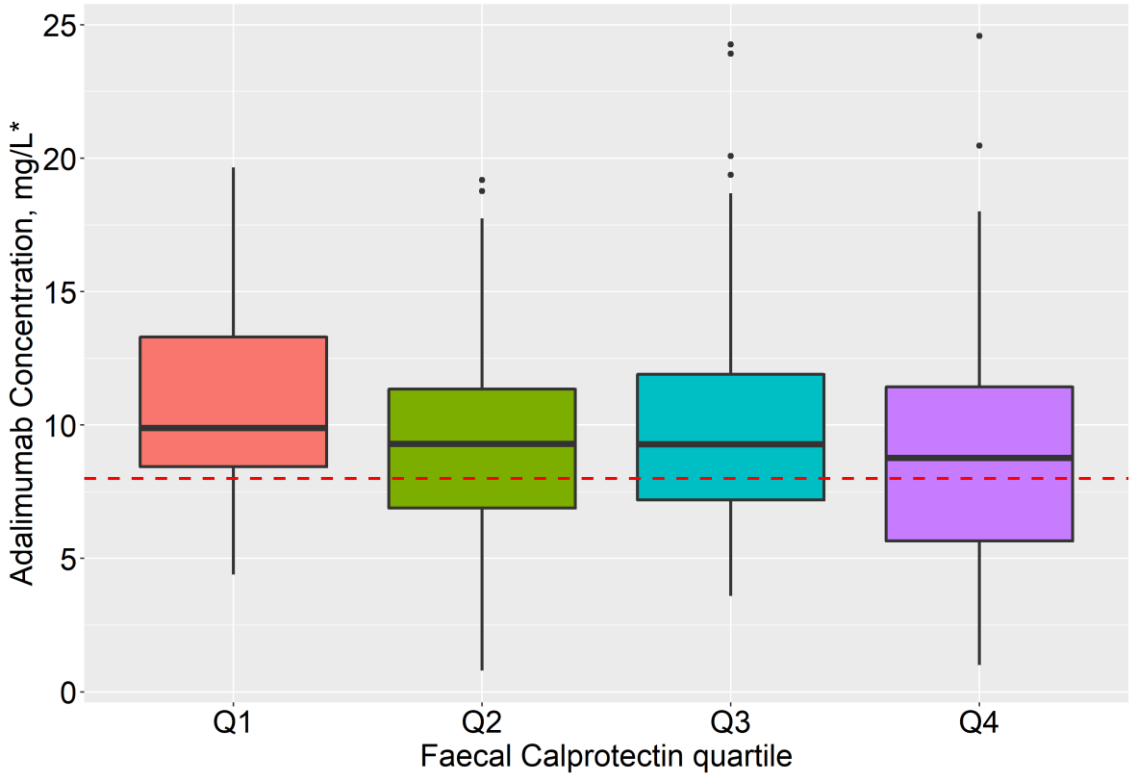


Supplementary 1. Prediction-corrected numerical predictive check (pcVPC) for the adalimumab serum concentrations in the external evaluation group at day 7 (left) and day 14 (right) after last dose. Red solid line, median of the observations; green solid line, median of the predictions; green dashed lines, 5th and 95th percentile of the predictions.



Supplementary 2. Observed adalimumab concentrations at steady state stratify by faecal calprotectin quartile. Red dotted line represents the therapeutic range for endoscopic remission (TASCs > 8 mg/L).

Supplementary Table 1. Descriptive statistics of adalimumab and faecal calprotectin at steady state stratified by faecal calprotectin quartiles

	Adalimumab concentrations (mg/L)				Faecal calprotectin (mg/kg)				Concentration ≤ 8 mg/L
Quartile	**Mean**	**SD**	**MIN**	**MAX**	**Mean**	**SD**	**MIN**	**MAX**	**Proportion**
FCP Q1	10.53	3.24	4.40	19.65	12.93	3.99	5.00	17.00	0.23
FCP Q2	9.73	4.16	0.80	19.19	45.67	14.98	18.00	73.00	0.37
FCP Q3	10.14	4.59	3.60	24.27	150.36	58.87	74.00	281.00	0.36
FCP Q4	9.21	4.52	1.00	24.58	923.57	725.64	286.00	3240.00	0.47

FCP, faecal calprotectin; SD, standard deviation; MIN, minimum; MAX, maximum

3. A 3-year prospective study of a multidisciplinary early proactive therapeutic drug monitoring programme of infliximab treatments in inflammatory bowel disease

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Revista

British Journal of Clinical Pharmacology. 2020; 86(6): 1165-1175.

DOI:10.1111/bcp.14229

Resumen

La monitorización terapéutica de las concentraciones séricas mínimas de infliximab se ha utilizado principalmente en el caso de pérdida de respuesta en pacientes con enfermedad inflamatoria intestinal. El objetivo de este estudio fue evaluar la eficacia y seguridad de un programa multidisciplinar de monitorización proactiva temprana para el ajuste de la dosis de infliximab.

Se realizó un estudio prospectivo de tres años de duración en el que se incluyeron 81 pacientes que comenzaron tratamiento con infliximab bajo el programa de monitorización, con el primer control en la semana 14 de tratamiento. Se incluyó un

grupo de control histórico de 72 pacientes tratados con el fármaco cuya dosificación fue optimizada empíricamente según respuesta. Las variables de eficacia fueron el fracaso del tratamiento, la cirugía y la hospitalización relacionadas con la enfermedad. Las variables de seguridad fueron reacciones infusionales graves y reacciones adversas. Se utilizó la regresión de Cox para el análisis de supervivencia.

En el grupo de estudio se encontró una reducción significativa en el riesgo de fracaso del tratamiento (hazard ratio [HR]: 0,51; intervalo de confianza [IC] del 95%: 0,27-0,92; p = 0,037), cirugía relacionada con EII (HR: 0,14; IC 95%: 0,03-0,65; p = 0,012) y hospitalización (HR: 0,38; IC 95%: 0,17-0,87; p = 0,022) respecto al grupo control. El número de reacciones infusionales graves fue menor en el grupo de pacientes monitorizados (2,5% vs 10,4%; p <0,050); mientras que la incidencia de reacciones adversas fue similar (3,7% vs 3,9%; p = 1,000).

Este estudio muestra que, en comparación con la dosificación empírica, la monitorización proactiva temprana se asocia con una mayor eficacia y seguridad de la terapia con infliximab, ya que reduce la hospitalización y las cirugías relacionadas con la enfermedad inflamatoria intestinal, la incidencia de reacciones infusionales graves, y aumenta la durabilidad a largo plazo de los tratamientos.

Received: 18 June 2019 | Revised: 10 January 2020 | Accepted: 18 January 2020

DOI: 10.1111/bcp.14229

ORIGINAL ARTICLE

A 3-year prospective study of a multidisciplinary early proactive therapeutic drug monitoring programme of infliximab treatments in inflammatory bowel disease

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Aims: Therapeutic drug monitoring (TDM) of trough serum infliximab concentrations has been mainly used in case of loss of response in patients with inflammatory bowel disease (IBD). The aim of this study was to evaluate the effectiveness and safety of a multidisciplinary early proactive TDM (mep-TDM) programme for dose adjustment.

Methods: A 3-year prospective study was conducted based on a sample of 81 patients who started treatment and were subsequently subjected to mep-TDM with the first control at week 14. Data of a historical control group of 72 patients treated with infliximab and managed with empirical dosing were included. Effectiveness variables were treatment failure, IBD-related surgery and IBD-related hospitalization. Safety variables were serious infusion reactions (SIRs) and adverse reactions. Cox regression was used for survival analysis.

Results: In the mep-TDM study group, compared to the control group, there was a significant reduction in the risk of treatment failure (hazard ratio [HR]: 0.51; 95% confidence interval [CI]: 0.27–0.92; P = .037), IBD-related surgery (HR: 0.14; 95% CI: 0.03–0.65; P = .012) and hospitalization (HR: 0.38; 95% CI: 0.17–0.87; P = .022). SIRs were lower in the mep-TDM group (2.5% *vs* 10.4%; P < .050); the incidence of adverse reactions was similar (3.7% *vs* 3.9%; p > .999).

Conclusion: This study found that compared to empirical dosing, mep-TDM is associated with improved efficacy and safety of infliximab therapy, reduced IBD-related hospitalization and surgery and incidence of SIRs, and increasing long-term durability of treatment effects.

KEYWORDS

inflammatory bowel diseases, infliximab, personalized medicine, therapeutic drug monitoring

1 | INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic process characterized by a disproportionate immune response that damages the tissues of the digestive tract and leads to injuries of different severity. Ulcerative colitis (UC) and Crohn's disease (CD) are the most common forms of IBD.[1,2] These pathologies share many similarities in terms of symptoms, risk factors and treatment, the main difference being the area of the digestive system where inflammation occurs: in UC only the mucosa of the large intestine or the colonic mucosa is affected, whereas in CD transmural lesions can occur in any part of the digestive tract.

The therapeutic use of anti-**tumour necrosis factor** (anti-TNF) monoclonal antibodies, such as **infliximab**, adalimumab, golimumab and certolizumab pegol, has dramatically changed the management of

The authors confirm that the principal investigator for this paper is Fernando Muñoz and that he had direct clinical responsibility for the patients.

IBDs.[3,4] However, although a high percentage of patients (70–90%) initially respond to treatment, loss of response (LOR) rates after induction are high (20–50%).[5,6] There are several reasons for this lack of response, 1 being the formation of anti-drug antibodies that bind to the epitope of the drug and form immune complexes that increase its clearance, leading to inferior clinical outcomes.[5,7,8] Additionally, lack of response can be associated with non-immune-related factors such as high body mass index, hypoalbuminaemia, high disease burden, and the location and/or size of the affected surface.[9,10] Pharmacodynamic factors such as alternative pathway (re)activation of inflammation may also lead to nonresponse.[4]

Currently, in clinical practice, pharmacological options after failure of these drugs are limited.[11] Once the lines of treatment have been exhausted, the only available alternative is surgery. Therefore, optimization of response in order to maintain treatment using standard anti-TNFs in the early stages for as long as possible has gained relevance in recent years, becoming the subject of numerous studies.[12-14]

Therapeutic drug monitoring (TDM) of anti-TNF has been traditionally used in patients with active inflammatory symptoms, this strategy being known as reactive TDM. Recent studies have assessed the usefulness of early proactive TDM[15-17] following an approach that involves determination of trough serum infliximab concentrations (TSIC) in all patients from the beginning of the treatment to optimize the dose by reaching target TSIC. Since low TSIC have been associated with an increased risk of anti-infliximab antibody (ATI) development, the potential clinical benefits of this type of monitoring include the prevention of immunogenicity and an increased probability of remaining longer on anti-TNF therapy.[10,14]

The objective of this study was to prospectively evaluate the long-term effectiveness and safety of a multidisciplinary early proactive TDM programme (mep-TDM) as a tool for infliximab dose adjustment in patients with IBD.

What is already known about this subject

- Therapeutic drug monitoring (TDM) of infliximab could be a useful tool for dose adjustment in the management of loss of response in inflammatory bowel disease.
- There are limited data on the usefulness of proactive TDM in patients from the beginning of treatment.

What this study adds

- Early proactive TDM improves the efficacy, safety and durability of treatments.
- Patients with inflammatory bowel disease on an empirical dosage of infliximab have a high probability of presenting subtherapeutic concentrations, associated with loss of response.
- Multidisciplinary teams, including experts with clinical pharmacokinetic experience to adequately interpret and present TDM results, contribute to achieve better outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design and population

In 2015, a mep-TDM of infliximab programme aimed at treatment optimization in IBD patients was started at our Centre by the Gastroenterology Service in collaboration with the Pharmacokinetics Laboratory of the Pharmacy Service. Over the previous 3 years, 76 patients had been subjected to infliximab therapy with dose adjustments based only on clinical response as the standard of care. This group was used as control, and TSICs and ATIs were measured for all the patients under treatment with infliximab at the time of the beginning of the prospective study.

After the implementation of the mep-TDM program, a 3-year prospective, longitudinal, cohort study was conducted from September 2015 to September 2018 using data from patients aged >18 years who started infliximab treatment and had been diagnosed with moderate or severe CD and UC according to the following criteria: Partial Mayo Clinic Score > 4 for UC[18] and Simplified Endoscopic Activity Score for CD >4 and/or Harvey–Bradshaw Index Score > 7 for CD.[19,20] The study was approved by the Local Ethics Committee and signed consent was obtained from all the patients who agreed to participate.

Patients with the following characteristics were excluded from the study: <14 weeks of treatment; isolated administration due to transfers to other centres; and isolated outbreaks. In all cases, the initial dose of infliximab was administered according to the recommendations provided in the drug data sheet: 5 mg kg^{-1} by intravenous infusion at weeks 0, 2, 6 and 14 (induction phase) and, subsequently, proactive TDM was used for dose adjustments. The use of concomitant immunosuppressants was allowed.

The following baseline variables were collected: age, sex, type of disease, extent of the disease, CD behaviour, age at diagnosis, age at start of infliximab, perianal fistulizing disease, concomitant use of immunomodulators (i.e. thiopurines or methotrexate), extraintestinal manifestations (musculoskeletal, dermatological, hepatopancreatobiliary or ocular), faecal calprotectin (FCP) and C-reactive protein (CRP) serum levels. Disease extent and behaviour were defined according to the Montreal Classification.[2]

2.2 | TDM strategy

During the study period, all patients who had started treatment with infliximab were proactively monitored, and the first TSIC was determined at week 14. TDM was repeated after 2 infliximab administrations in those patients who had required dose adjustment, to verify that target TSICs had been reached. Once TSICs were within therapeutic range, TDM was routinely performed every 6 months. Figure 1 shows the algorithm used for making therapeutic decisions based on TSICs and clinical response. This was adapted from the

algorithm initially designed at our centre for TDM of anti-TNF agents.[12]

TSICs and ATIs were determined by ELISA (Promonitor) in the Pharmacokinetics Laboratory of our centre. In this technique, serum infliximab binds to TNF and is detected by an anti F (ab')2-infliximab, horseradish peroxidase-labelled antibody. The disadvantages of this assay are that it is a drug-sensitivity test that cannot detect drug-bound ATI[21] and that it lacks specificity to distinguish between biologically functional and nonfunctional ATIs.

The TSIC therapeutic range was established according to the available literature: 5–10 μg mL^{-1} at week 14 of treatment[12] and 3–10 μg mL^{-1} during the maintenance phase.[13-15,22] Concentrations above 10 μg mL^{-1} were used in patients with CD and perianal fistulizing disease.[23] ATIs were measured in patients with TSIC <1 μg mL^{-1}.[12,24]

TSICs were obtained in the hours prior to the administration of infliximab. However, in patients with inflammatory symptoms, mostly when low TSICs were suspected, additional samples were taken during the administration interval in order to make the optimal therapeutic decision.

Prior to the beginning of the study, a preliminary population pharmacokinetic model of infliximab in adult patients with IBD had been developed. For this purpose, a nonlinear mixed effects modelling using the first-order conditional estimation method with interaction was used to develop the population pharmacokinetic model using NONMEM version 7.3.0 (Icon Development Solutions, Ellicott City, MD, USA). Patient characteristics and bi-compartmental model specifications can be found in Appendix 1. In our preliminary pharmacokinetic model, body weight, FCP and ATIs proved to be the variables with the most significant impact on infliximab pharmacokinetics.

Optimal individualized dosage estimation was addressed using a Bayesian approach based on TSICs, demographical information and other patient characteristics to predict TSIC evolution over time. A priori information (IFX population pharmacokinetic parameters) was combined with a posteriori information (individual TSICs) to predict future concentrations.[25] Individual pharmacokinetic parameters were estimated and subsequently used to predict the optimal individualized dosing (dose and interval) required to reach therapeutic TSICs. For this purpose, infliximab concentrations were simulated based on nonlinear mixed effects modelling (NONMEM version 7.3.0). Then, this information, together with the clinical and endoscopic outcomes, was used to draw up a pharmacokinetic report with the patient-adapted dosage recommendation.

2.3 | Therapeutic outcomes

Loss of response was defined as worsening or relapsing of symptoms, that is, Harvey–Bradshaw Index Score >4 in CD, partial Mayo clinic score > 2 in UC, biological activity (FCP >100 mg Kg^{-1} or CRP level > 0.5 mg dL^{-1}), together with endoscopic or radiological findings of active disease. Endoscopies were performed according to clinical criteria.

The effectiveness variables were treatment failure (TF), IBD-related surgery and IBD-related hospitalization during the first 3 years from the beginning of treatment. The follow-up period for IBD-related surgery and IBD-related hospitalization was extended 6 months beyond infliximab discontinuation provided that no other biological drug was administered in the meantime.

Reasons for TF were LOR despite therapeutic TSICs, severe infusion-related reactions (SIRs), adverse reactions (ARs) or nonreversible ATIs.

IBD-related surgery included total or partial bowel resection, ostomy, ileal pouch-anal anastomosis. Fistula seton placement and

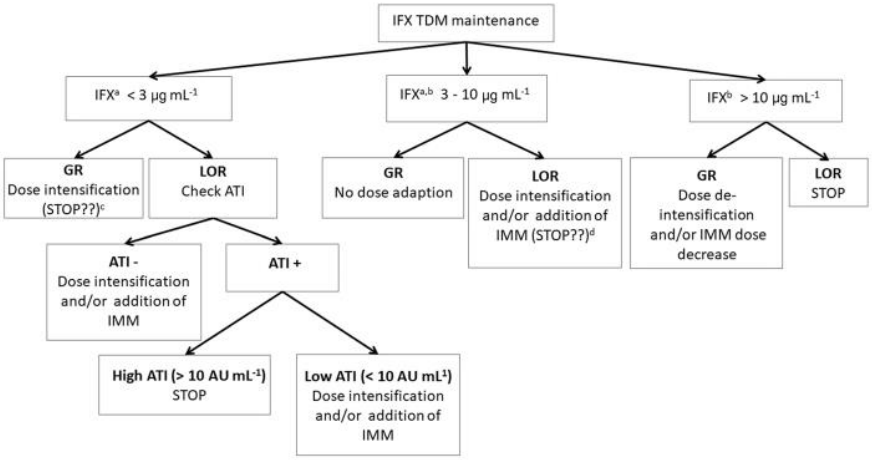


FIGURE 1 Algorithm designed to make therapeutic decisions based on trough serum concentrations of infliximab, presence of anti-infliximab antibodies and treatment response. Response is based on clinical, endoscopic and biochemical outcomes. Adapted from reference 12

ATI: anti-infliximab antibodies; GR: good response; IFX: infliximab; IMM: immunosuppressants; LOR: loss of response; TDM: therapeutic drug monitoring.
a: 5 μg mL^{-1} at week 14th.
b: 10-15 μg mL^{-1} perianal fistulizing Crohn disease.
c: patients in endoscopic remission for a long time and infra-terapeutics trough concentrations of IFX could be candidates for drug holiday.
d: patients with trough concentrations in the upper zone of the therapeutic range are unlikely to benefit from dose intensification.

abscess drainage were excluded from IBD-related surgery. By contrast, IBD-related hospitalization was defined as any hospitalization due to relapse, intestinal obstruction, fissure, symptomatic fistula, abscess or gastrointestinal symptoms secondary to IBD, such as abdominal pain, diarrhoea, constipation or gastrointestinal bleeding.

To evaluate the effect of mep-TDM on drug safety, the number of patients with SIRs and ARs during the first 3 years after starting the treatment with infliximab was compared in both groups.

2.4 | Statistical analysis

Descriptive statistics were provided using median or mean for the continuous variables, and frequency and percentage for the categorical variables. The continuous variables were compared using *t*-test or Wilcoxon test, and the categorical variables using the χ^2 test or Fisher's exact test, as appropriate.

Kaplan–Meier estimates were used to draw the cumulative and incidence curves of probability of TF, IBD-related surgery and IBD-related hospitalization. Curves were compared using the log-rank test. Additionality, a subgroup analysis was made in order to evaluate the effectiveness variables on CD and UC patients.

Univariate and multivariate survival analysis using Cox proportional-hazards regression was performed to determine the independent effects of different variables that could be associated with the therapeutic outcomes. The examined variables were sex, age at diagnosis, age at start of infliximab treatment, IBD subtype, UC extension, CD location and behaviour, perianal fistulizing disease, concomitant use of immunomodulators, and extraintestinal manifestations. Variables were eliminated from the multivariate model if Wald test results rendered them nonsignificant ($P < .1$). All *P*-values were based on a 2-sided hypothesis, and those <.05 were considered statistically significant.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[26] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[27]

3 | RESULTS

3.1 | Therapeutic drug monitoring in empirically dosed patients

Prior to the beginning of the study, 52 patients were already under chronic infliximab therapy. The results obtained from these patients are shown in Figure 2. Dose adjustment according to standard care revealed that 48.1% of the patients had subtherapeutic TSICs and 13.5% had ATIs. The average TSIC (standard deviation) measured was 4.35 (4.40) μg mL^{-1}.

These results were taken into account to manage the dosage regimens. Dose escalation (interval decrease and/or dose increase) was performed in 18 patients with subtherapeutic TSICs. Infliximab was discontinued in 7 patients with subtherapeutic TSICs and high levels of ATIs. Additionally, infliximab treatment was switched to adalimumab in 3 other patients with low TSICs who were already receiving exceptionally high intensified empirical doses. By contrast, a treatment de-escalation was carried out in 6 patients with supratherapeutic TSICs. For this purpose, an extended interval was selected.

It must be pointed out that treatment was escalated in 4 patients with therapeutic levels of TSICs due to inadequate response, whereas infliximab treatment was switched to vedolizumab in 1 patient due to TSIC being in the upper limit of the therapeutic range and a lack of clinical control.

3.2 | Early proactive therapeutic drug monitoring

Mep-TDM was performed on 81 patients who started infliximab, and a total of 201 TSICs were determined over a 3-year period. The median (interquartile range) follow-up of patients was 82 (34–118) weeks. The clinical and demographic characteristics of the study and control group patients are presented in Table 1. As shown, patient characteristics at the time of inclusion in the study were similar in both groups and, therefore, comparable.

Patients who started treatment with infliximab during the study were proactively monitored, with initial TDM at week 14. Table 2 shows the main data related to the mep-TDM programme. Among the

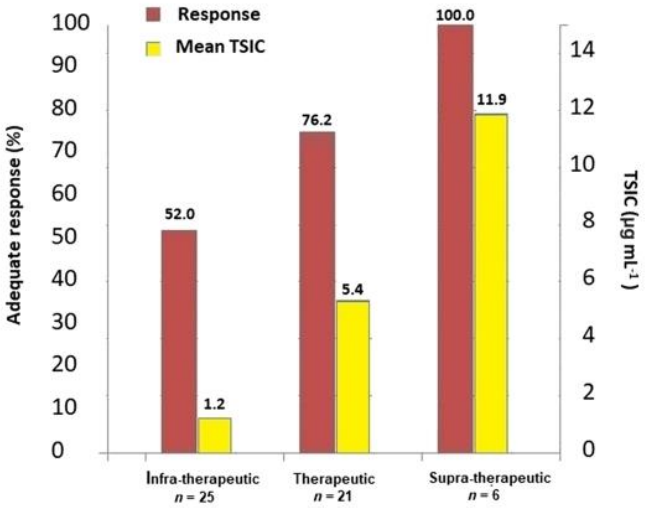


FIGURE 2 Serum infliximab concentrations and corresponding clinical response obtained in 52 patients of the control group managed with standard of care. TSIC: trough serum infliximab concentrations; supratherapeutic: TSIC <3 μg mL^{-1}; therapeutic: TSIC 3–10 μg mL^{-1}; supratherapeutic: TSIC >10 μg mL^{-1}

monitored patients, 33 (40.7%) and 6 (7.4%) required early dose adjustment because of low and high TSICs, respectively. Furthermore, 2 patients developed reversible ATIs, and 1 with therapeutic levels of TSIC presented primary TF and had to be treated with vedolizumab. Over the 3-year follow-up period, out of the patients subjected to mep-TDM, 51 (63%) underwent dose escalation and 28 (35%) received de-escalation in order to reach the therapeutic range. By contrast, 26 patients (32%) received no dose modification during the study.

Figure 3 shows the Kaplan–Meier cumulative probability curves for TF, IBD-related surgery and IBD-related hospitalization. Patients who underwent mep-TDM had a statically higher probability of maintaining treatment with infliximab and a significantly lower cumulative probability of IBD-related surgery and IBD-related hospitalization than those who were not subjected to TDM. In the subgroup analysis, the survival curves of patients with CD and UC showed a similar behaviour and no statistically significant differences were found.

A lower number of TFs was observed among the patients subjected to mep-TDM: 15 (18.5%) of the patients in the study group *vs* 30 (39.5%) in the control group. Reasons for treatment discontinuation in the mep-TDM group were: 8 inadequate clinical responses (9.9%), 4 ATIs (4.9%), 2 ARs (2.5%) and 1 SIR (1.2%). In the control group, 18 (23.7%), 7 (9.0%), 3 (3.9%) and 2 (2.6%) treatments were discontinued due to inadequate clinical response, SIRs, ARs and other, respectively. The median time for the appearance of ATIs in the study group was 27 weeks in a range between 15 and 42 weeks.

Table 3 shows the results from univariate and multivariate Cox analysis for TF. Univariate Cox analysis showed a lower probability of TF compared with the control group (hazard ratio [HR] = 0.53; 95%

TABLE 1 Baseline characteristics of patients included in the study

		Control group	Early proactive TDM group	*P* value
n		76	81	
Sex, male (%)		38 (50.0)	48 (59.3)	.32
Age at diagnosis (y), median (IQR)		29 (20–38)	32 (20–42)	.22
Age at start of infliximab (y), median (IQR)		38 (24–49)	41 (29–50)	.17
Weight (kg), median (IQR)		67.8 (57–80)	69.4 (56–82)	.63
Body mass index (kg m^{-2}), median (IQR)		24.2 (21.1–27.5)	24.6 (21.4–28.0)	.58
IBD type	**CD, *n* (%)**	61 (80.3)	56 (69.1)	.16
	UC, *n* (%)	15 (19.7)	25 (30.9)	
CD Location[a]	**L1 (ileal), *n* (%)**	30 (49.2)	33 (58.9)	.71
	L2 (colonic), *n* (%)	8 (13.1)	4 (7.2)	
	L3 (ileocolonic), *n* (%)	23 (37.7)	19 (33.9)	
	L4 (upper GI disease), *n* (%)	2 (3.3)	1 (1.8)	
CD behaviour	**B1 (nonstricturing, nonpenetrating), *n* (%)**	23 (37.7)	26 (46.4)	.62
	B2 (stricturing), *n* (%)	8 (13.1)	7 (12.5)	
	B3 (penetrating), *n* (%)	30 (49.2)	23 (41.1)	
Perianal fistulizing disease, *n* (%)		19 (25.0)	14 (17.3)	.32
UC extent	**E1 (proctitis), *n* (%)**	3 (20.0)	9 (36.0)	.56
	E2 (left-side colitis), *n* (%)	3 (20.0)	4 (16.0)	
	E3 (pancolitis), *n* (%)	9 (60.0)	12 (48.0)	
Extraintestinal manifestations, *n* (%)		28 (36.8)	24 (29.6)	.72
	Musculoskeletal, *n* (%)	22 (28.9)	19 (23.5)	
	Dermatologic, *n* (%)	4 (5.3)	1 (1.2)	
	Other, *n* (%)	2 (2.6)	4 (4.9)	
Concomitant IMM at start of infliximab, *n* (%)		59 (77.6)	60 (74.1)	.73
	Thiopurines (azathioprine, 6-MP), *n* (%)	53 (69.7)	57 (7.4)	
	Methotrexate, *n* (%)	6 (7.9)	3 (3.7)	
CRP at diagnosis (mg dL^{-1}), median (IQR)		1.1 (0.1–3.1)	1.3 (0.1–3.7)	.72
FCP at diagnosis (mg kg^{-1}), median (IQR)		NA	222.0 (15–3590)	-

ATI: antidrug antibody; CD: Crohn's disease; CRP: C-reactive protein; FCP: faecal calprotectin; GI: gastrointestinal; IBD: inflammatory bowel disease; IMM: immunomodulators; NA: not available; TDM: therapeutic drug monitoring; UC: ulcerative colitis.

[a] Patients could present several locations (L) of the CD lesion.

TABLE 2 Early proactive therapeutic drug monitoring outcomes

n	81
Duration of infliximab treatment (wk), median (IQR)	82 (34–118)
TSICs analysed during the study, *n*	201
TSIC at week 14 (μg mL^{-1}), median (IQR)	5.8 (2.2–7.8)
Therapeutic, *n* (%)	42 (51.9)
Supratherapeutic, *n* (%)	6 (7.4)
Subtherapeutic, *n* (%)	33 (40.7)
Immunogenic TSIC (< 1 μg mL^{-1}), *n* (%)	6 (7.4)
ATI at week 14, *n* (%)	2 (2.5)
Optimized treatments per patient (n y^{-1}), median (IQR)	1 (0–2)
Optimized dose during the study (mg kg^{-1}), median (IQR)	5.1 (5.0–5.9)
Optimized interval during the study (wk), median (IQR)	7 (5–8)
Non reversible ATI during the study, *n* (%)	4 (4.9)
Severe infusion-related reactions, *n* (%)	2 (2.5)
Non infusion-related adverse reactions, *n* (%)	3 (3.7)

ATI: antidrug antibody; IQR: interquartile range; TSIC: trough serum infliximab concentrations.

confidence interval [CI]: 0.28–0.97; $P < .05$) with 3-year absolute risk reduction (ARR) of 23%. Mep-TDM (HR = 0.51; 95% CI: 0.27–0.92; $P < .05$) and extraintestinal manifestations (HR = 1.72; 95% CI: 1.02–3.16; $P < .05$) were the only variables independently associated with TF.

Patients who underwent mep-TDM were less liable to require IBD-related surgery (2 in the study group *vs* 16 in the control group) and 3-year ARR was 25%. Multivariate analysis (Table 4) yielded significantly lower values for IBD-related surgery with the use of mep-TDM (HR = 0.14; 95% CI: 0.03–0.65; $P < .05$), whereas perianal fistulizing disease increased the risk (HR = 3.13; 95% CI: 1.17–8.42; $P < .05$).

Eight patients under mep-TDM had to be admitted for IBD-related hospitalization against 23 from the control group. By the end of the follow-up period, the 3-year ARR of IBD-related hospitalization was 23% in the study group. Mep-TDM was the only variable associated with IBD-related hospitalizations (HR = 0.38; 95% CI: 0.17–0.87; $P < .05$). All univariate and multivariate analysis results are shown in Table 5.

The apparently high percentage of patients receiving concomitant immunosuppressant therapy at the start of infliximab treatment led to the decision to analyse the effect of these drugs on the effectiveness variables. As shown in Tables 3–5, concomitant immunosuppressant therapy was not associated with TPF, IBD-related hospitalization or surgery. In addition, a supplementary analysis comparing all the patients with concomitant immunosuppressant *vs* monotherapy infliximab yielded no statistically significant differences: HR: 1.09, 95% CI: 0.54–2.20, $P = .81$ for TF; HR: 2.58, 95% CI 0.59–11.25, $P = .21$ for IBD-related surgery; and HR = 1.55, 95% CI: 0.59–4.04, $P = .37$ for IBD-related hospitalization.

In relation to the effect of mep-TDM on treatment safety, SIRs were significantly lower in patients under mep-TDM (2.5 *vs* 10.4%; $P = .048$), but the onset of ARs was similar in both groups (3.7% and 3.9%, respectively; $P > .999$).

4 | DISCUSSION

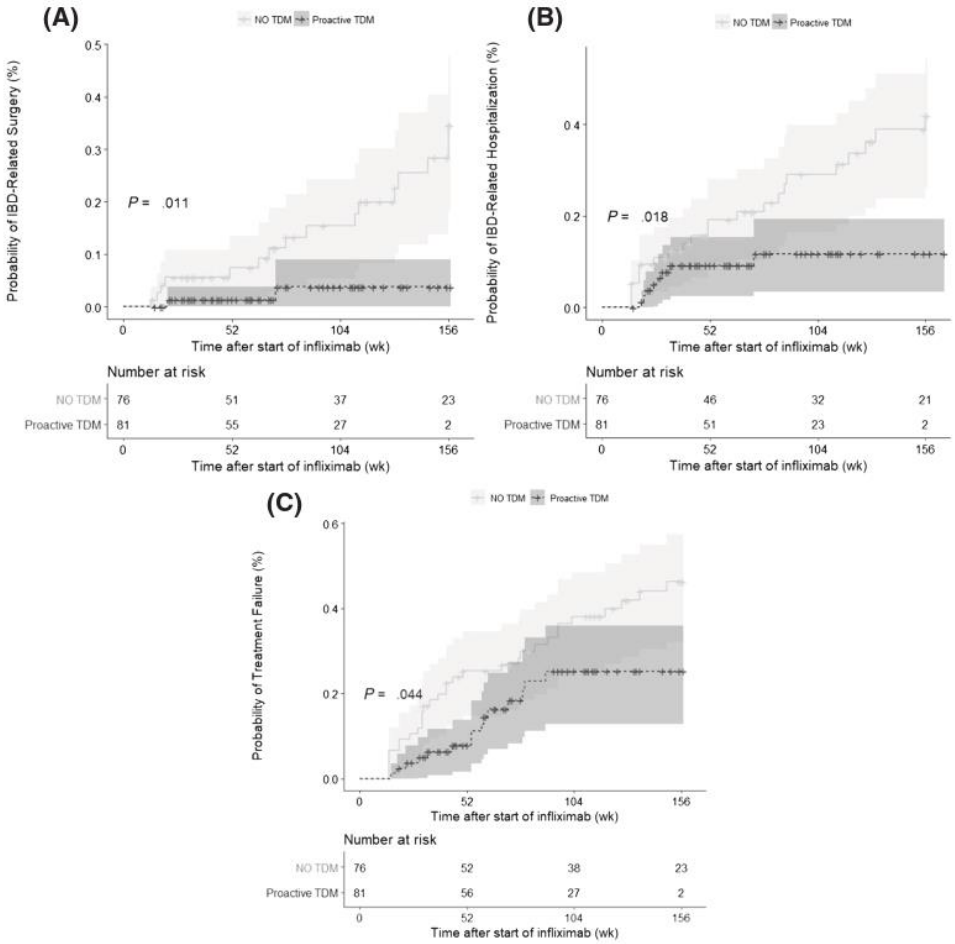
Pharmacokinetic variability is a well-known key source of variability in anti-TNF response.[28] In addition, there is increasing evidence that higher infliximab levels are associated with sustained response and, likewise, low or undetectable TSICs increase the likelihood of LOR.[29] Therefore, TDM is emerging as a useful therapeutic tool to facilitate personalization of these treatments.[29-31]

In our study, patients subjected to empirical therapy had a low probability of reaching therapeutic TSICs (40.4%). Furthermore, a positive correlation between TSICs and favourable therapeutic outcomes was observed (Figure 2). ATIs were also detected in a high number of patients (13.5%), which is probably connected to the high percentage (48.1%) of patients with subtherapeutic TSICs. These results are consistent with previous studies.[29,32-34] Our findings underscore the convenience of guiding therapeutic decisions through personalized dosing in order to reach the desired TSICs and maximize positive therapeutic outcomes.

From the start of the study, proactive TDM was considered as the dosing guide strategy for all the patients in our centre. We found that patients with mep-TDM had 23% cumulative probability of TF 3 years from the beginning of the treatment. This probability was significantly lower ($P < .05$) than that observed in the control group (46%). In addition, cumulative risks of IBD-related surgery and IBD-related hospitalization became significantly reduced after implementing the mep-TDM program, as presented in Figure 3: surgery from 28 to 3% ($P < .05$) and hospitalization from 32 to 9% ($P < .05$). The low percentage of patients with circulating ATIs (4.9%) observed after the implementation of TDM probably contributed towards achieving these better results.[35]

Papamichael et al.[16] based on a sample of 130 patients with IBD under proactive TDM, estimated an accumulative probability of 85% of them remaining on infliximab 3 years after starting the treatment and a cumulative risk of IBD-related surgery and IBD-related hospitalization of 5 and 9%, respectively. In this study, the first TDM session was performed after a median time of >1 year of infliximab therapy. Therefore, the sample population could have influenced the slightly improved results in relation to our study. Vaughn et a.[17] also observed that IBD patients under proactive TDM had a greater probability of remaining on infliximab after 3 years than those receiving infliximab doses at the discretion of the treating physician, this probability increasing in patients who achieved TSIC >5 μg mL^{-1}.

The similarity among the survival curves shown in all the studies carried out in IBD patients is worth noting. During the first 2 years after the start of infliximab treatment, a pronounced slope is observed; however, after this period, the curves become flat, probably



CI: confidential interval: HR: hazard ratio; IBD: inflammatory bowel disease; TDM: therapeutic drug monitoring.

FIGURE 3 Kaplan–Meier cumulative probability curves for inflammatory bowel disease (IBD)-related surgery (A) IBD-related hospitalization (B) and probability of treatment failure with infliximab (C) in patients with early proactive therapeutic drug monitoring (TDM) and control group, respectively

TABLE 3 Univariate and multivariate analysis of infliximab treatment failure

	Univariate Cox analysis HR (95% CI)	*P*	Multivariate Cox analysis HR (95% CI)	*P*
Proactive TDM	0.53 (0.28–0.97)	.042	0.51 (0.27–0.92)	.037
Sex (ref male)	1.02 (0.57–1.84)	.924	-	
Diagnosis (ref UC)	0.79 (0.42–1.50)	.477	-	
Perianal fistulizing disease	0.88 (0.43–1.83)	.734	-	
Age at diagnosis	1.02 (0.68–1.52)	.916	-	
Age at start of infliximab	1.33 (0.84–2.12)	.224	-	
CD localization (ref L1)	0.99 (0.69–1.44)	.978	-	
CD behaviour (ref B1)	0.91 (0.56–1.48)	.713	-	
UC extension (ref E1)	1.64 (0.60–0.79)	.182	-	
Concomitant use of immunomodulators	1.09 (0.54–2.20)	.806	-	
Extraintestinal manifestations	1.75 (0.98–3.13)	.057	1.72 (1.02–3.16)	.044

CD: Crohn's disease; CI: confidence interval; HR: hazard ratio; TDM: therapeutic drug monitoring; UC: ulcerative colitis.

TABLE 4 Univariate and multivariate analysis of surgery related with inflammatory bowel disease

	Univariate Cox analysis HR (95% CI)	*P*	Multivariate Cox analysis HR (95% CI)	*P*
Proactive TDM	0.18 (0.04–0.79)	.023	0.14 (0.03–0.65)	.012
Sex (ref male)	2.28 (0.79–1.10)	.275	-	
Diagnosis (ref UC)	1.62 (0.60–4.37)	.335	-	
Perianal fistulizing disease	2.73 (1.08–6.95)	.024	3.13 (1.17–8.42)	.015
Age at diagnosis	1.25 (0.63–2.49)	.515	-	
Age at start of infliximab	1.88 (0.80–4.39)	.146	-	
CD localization (ref L1)	0.15 (0.03–0.69)	.015	-	
CD behaviour (ref B1)	1.40 (0.23–8.30)	.708	-	
UC extension (ref E1)	1.34 (0.66–2.72)	.411	-	
Concomitant use of immunomodulators	2.18 (0.49–9.63)	.303	-	
Extraintestinal manifestations	1.79 (0.67–4.78)	.244	-	

CD: Crohn's disease; CI: confidence interval; HR: hazard ratio; TDM: therapeutic drug monitoring; UC: ulcerative colitis.

TABLE 5 Univariate and multivariate analysis of hospitalization related with inflammatory bowel disease

	Univariate Cox analysis HR (95% CI)	*P*	Multivariate Cox analysis HR (95% CI)	*P*
Proactive TDM	0.38 (0.17–0.87)	.022	0.38 (0.17–0.87)	.022
Sex (ref male)	0.88 (0.37–2.10)	.779	-	
Diagnosis (ref UC)	1.24 (0.57–2.67)	.591	-	
Perianal fistulizing disease	1.93 (0.91–4.10)	.088	-	
Age at diagnosis	1.01 (0.59–1.73)	.962	-	
Age at start of infliximab	1.02 (0.57–1.84)	.931	-	
CD localization (ref L1)	0.81 (0.49–1.35)	.423	-	
CD behaviour (ref B1)	2.86 (0.80–10.20)	.105	-	
UC extension (ref E1)	1.10 (0.59–2.05)	.763	-	
Concomitant use of immunomodulators	1.29 (0.49–3.42)	.611	-	
Extraintestinal manifestations	1.11 (0.51–2.46)	.785	-	

CD: Crohn's disease; CI: confidence interval; HR: hazard ratio; TDM: therapeutic drug monitoring; UC: ulcerative colitis.

because the development of antibodies occurs mainly during these first months.[36] In our study group, ATIs were only detected in this period.

Consistent with other studies,[13,16,36] we found a low incidence of SIRs (2.5%) in patients subjected to mep-TDM, whereas the percentage was significantly higher in the control group (10.4%). These results, in turn, could be related to the low proportion of patients with ATIs, since there is evidence that the development of antibodies may complement anaphilotoxin activation and production.[36] However, as expected, the incidence of adverse reactions linked to the drug was similar in both groups. Our results support the association of immunogenicity and SIRs, suggesting a potential relationship between subtherapeutic TSICs and adverse effects, as well as the usefulness of mep-TDM to improve the safety profile of infliximab therapy.

In the study group, a population TDM-based Bayesian dose prediction was used, which provides a more efficient guide for dose adjustments.[37] This strategy incorporates data from TSICs, demographics and other patient's characteristics to predict the TSICs evolution over the time. TDM-based Bayesian dose prediction allowed TSICs within the therapeutic range to be reached in all new patients early after the induction phase. The high percentage of patients who yielded subtherapeutic TSICs at week 14 could indicate the convenience of conducting the first TDM during the induction phase, where higher TSICs are probably needed.[38]

Early proactive TDM is not yet a widespread practice, and reactive TDM in response to suboptimal disease control is emerging as the new standard of care for optimizing anti-TNF therapy in IBD.[29] By contrast, preliminary data that prove the usefulness of proactive TDM to improve therapeutic outcomes have been published and there are currently experts who believe that proactive TDM, which helps to optimize infliximab therapy before immunogenicity and/or LOR, should become standard clinical practice.[16,17,39-41]

At our centre, mep-TDM has proved effective in reducing IBD-related surgery and hospitalization, as well as in increasing the

durability of infliximab treatment, preventing changes to second-line treatments associated with higher direct costs. The analysis of 201 samples during a 3-year period of mep-TDM applied to infliximab dosing optimization in 81 patients showed that the potential benefits of proactive TDM outweigh the high cost of infliximab and ATIs determination and, consequently, mep-TDM could be a cost-effective strategy. A randomized prospective trial is yet to be carried out to confirm these results.

To ensure full clinical benefit of biological therapies, drug concentration measurements should be appropriately implemented and adequately interpreted. Many factors should be considered in the interpretation of TSIC, such as biological matrix, analytic variability, sampling time, variability pharmacokinetics, among others, which demand the involvement of experts with sufficient knowledge and training to adequately interpret and present TDM results.[42]

Multidisciplinary work is considered good practice in the healthcare system and the presence of multidisciplinary teams is well established in many healthcare institutions.[43] This involves the coordinated efforts of specialists with expertise in their corresponding areas, the combination of their skills being a key aspect in helping to improve health outcomes. In our shared-responsibility collaborative approach, doses were adapted to all the patients as required, and no patients needed additional visits or had wait for the next dose to adjust their treatment, unlike the experience reported in other studies.[13,44] Two recent surveys have yielded great heterogeneity in the use of TDM of biological agents in clinical practice, identifying the greatest barriers to their implementation.[44,45] Samaan et al.[45] revealed that many clinicians lack confidence in their TDM knowledge and conclude that TDM results should be interpreted according to clinical context and, ideally, by a multidisciplinary team. While our study was not designed to assess the benefits of multidisciplinary team work, the involvement of experts with sufficient knowledge and training to adequately interpret the results obtained in the laboratory, present the TDM results and get involved in the decision-making process has unquestionably contributed greatly towards the achievement of the clinical benefits expected from our mep-TDM.

The available data that suggest the usefulness of proactive TDM are mainly the result of retrospective studies. Therefore, a strength of this study is that the data are largely prospective, coming from real-life clinical practice and nonbiased with respect to patient selection, since the treatment management strategy used (mep-TDM) was the same throughout the entire study.

However, among the limitations of the study are its non-randomized nature and the use of historical population in the control group. Thus, the results should be confirmed by means of a prospective randomized controlled trial. Nonetheless, although this is considered the gold standard of study design, it is limited by several factors, such as resources, cost or even ethical standards. Another potential limitation is the use of a drug-sensitivity assay, which means that ATIs cannot be measured in presence of the drug; however, different reports conclude that drug-tolerant assays do not offer clinical benefits over drug-sensitivity assays.[16,29,42]

In conclusion, empirical doses of infliximab in IBD patients result in a high percentage of subtherapeutic TSICs and ATI development. An early proactive-TDM programme after the induction phase improves the long-term outcomes of infliximab therapy, increasing durability of the drug, decreasing IBD-related hospitalization and surgery and reducing ATIs and SIRs. Therefore, our preliminary results support the use of proactive TDM and, according to our experience, multidisciplinary care is a useful approach to personalize infliximab therapy for IBD patients.

ACKNOWLEDGEMENTS

The authors want to thank the support received from all the staff of our Pharmacokinetics Laboratory and the Pharmacy and Gastroenterology Services.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

J.G.S.H., N.R. and M.V.C. conceived and designed the study. F.M. selected and had direct clinical responsibility for patients. J.G.S.H. analysed the data. J.G.S.H., N.R., M.V.C. and A.M.S. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Sánchez-Hernández JG, Rebollo N, Martin-Suarez A, Calvo MV, Muñoz F. A 3-year prospective study of a multidisciplinary early proactive therapeutic drug monitoring programme of infliximab treatments in inflammatory bowel disease. *Br J Clin Pharmacol*. 2020;86:1165–1175. https://doi.org/10.1111/bcp.14229

APPENDIX 1

POPULATION PHARMACOKINETIC MODEL (POPPK)

A. Patient characteristics		
No. of patients		108
No. of serum samples		313
ATI, *n* (%)		26 (8.3)
Age (y), median (IQR)		42 (18–79)
Weight (kg), median (IQR)		70 (55–82)
Female, *n* (%)		51 (48,6)
IBD type	CD, *n* (%)	84 (77.8)
	UC, *n* (%)	24 (22.2)
Albumin (g dL^{-1}), median (IQR)		4.4 (4.1–4.9)
C-reactive protein (mg dL^{-1}), median (IQR)		0.40 (0,10–0.95)
FCP (mg kg^{-1}), median (IQR)		125 (20–580)

B. Pharmacokinetic parameters estimated and validation		
Parameters	Final Model Estimate (%RSE)	Bootstrap (*n* = 1000) Mean (95% CI)
CL (L h^{-1})	0.0158 (6%)	0.0159 (0.0141–0.176)
Vc (L)	4.8 (15%)	4.9 (3.3–6.2)
Vp (L)	4.13*	--
Q (L h^{-1})	0.30*	--
ATI-CL	4.24 (7%)	4.02 (1.71–7.56)
WGT-CL	0.177 (34%)	0.182 (0.03–0.388)
FCP-CL	0.0175 (28%)	0.0178 (0.0080–0.0269)
IIV-CL (CV, %)	22.8 (9%)	22.6 (19.1–25.9)
RUV (CV, %)	34.1 (11%)	33.6 (30.7–37.0)

$CLi = CL^* (WGT/70)^{WGT\text{-}CL} * (FCP/125)^{FCP\text{-}CL} * ATI\text{-}CL^{ATI}$

If detectable anti-infliximab antibodies, ATI-CL = 1, else ATI-CL = 0.

*Fixed parameters according Fasanmade et al., 2009.

ATI: anti-infliximab antibody; CD: Crohn's disease; CI: confidence interval; CL: clearance; CV: coefficient of variation; FCP: faecal calprotectin (mg kg^{-1}); IBD: inflammatory bowel disease; IQR: interquartile range; IIV-CL: interindividual variability on clearance; Q: intercompartment clearance; RSE: residual standard error; RUV: residual unexplained variability; UC: ulcerative colitis; Vc: central volume of distribution; Vp: peripheral volume of distribution; WGT: body weight (kg).

IV. DISCUSIÓN

Los fármacos biológicos anti-factor de necrosis tumoral alfa (anti-TNF), tales como infliximab y adalimumab, introdujeron en la pasada década un nuevo paradigma en el tratamiento de la enfermedad inflamatoria intestinal (EII) y han contribuido a mejorar notablemente el curso clínico, pronóstico y calidad de vida de estos pacientes, especialmente en aquellos refractarios, dependientes o intolerantes a los tratamientos convencionales[1]. Sin embargo, el uso de los anti-TNF, plantea el gran reto de la optimización posológica en los pacientes que no presentan adecuada respuesta terapéutica. Aproximadamente el 30% de los pacientes no responden al tratamiento en la fase de inducción, lo que se conoce como fallo primario, y casi un 50%, aunque presentan una respuesta inicial adecuada, deben interrumpir el tratamiento durante la fase de mantenimiento. Este hecho normalmente es debido a una pérdida secundaria de respuesta, que habitualmente se produce durante el primer año de tratamiento, o a la aparición de efectos adversos graves tales como las reacciones infusionales agudas o infecciones[2]. Tanto el fallo primario como la pérdida secundaria de respuesta se atribuyen principalmente al desarrollo de anticuerpos anti-fármaco (AAF), a concentraciones infraterapéuticas del fármaco o al predominio de un proceso inflamatorio independiente del TNF, es decir, pueden ser ocasionados por problemas farmacocinéticos y/o farmacodinámicos[3].

La respuesta clínica a las dosis estandarizadas de los fármacos anti-TNF no es por tanto universal y una gran parte de esta variabilidad en la respuesta se atribuye a la alta variabilidad farmacocinética (PK) individual[4,5]. De hecho, en los últimos años, varios estudios han mostrado la asociación entre la concentración de estos fármacos y el beneficio terapéutico. En este sentido, concentraciones elevadas de infliximab y adalimumab se han asociado con mayor probabilidad de conseguir una buena respuesta sostenida. Por el contrario, concentraciones bajas o indetectables se asocian con una mayor probabilidad de pérdida de respuesta y de inmunogenicidad[5,6]. Por lo tanto, la monitorización farmacocinética (TDM) de estos fármacos se está consolidando como

una herramienta de gran utilidad terapéutica para facilitar la optimización de estos tratamientos[3-6].

En la actualidad, la TDM de los tratamientos biológicos anti-TNF en EII constituye una herramienta de soporte a las decisiones clínicas que permite adaptar la dosificación a los requerimientos de cada paciente. El paciente puede así beneficiarse de una respuesta adecuada y duradera al tratamiento. Su utilidad clínica se centra en tres situaciones diferentes:

- Tratamiento de inducción, detectando concentraciones inadecuadas del anti-TNF para disminuir la probabilidad de fallo primario al tratamiento.

- Tratamiento de mantenimiento, optimizando el régimen de dosificación reduciendo la probabilidad de pérdida de respuesta secundaria.

- Pérdida de respuesta, ayudando a establecer las causas de la misma.

La modalidad más aceptada de monitorización de anti-TNF es aquella que se realiza a pacientes con pérdida de respuesta al tratamiento. Esta estrategia se denomina reactiva. Por el contrario, la monitorización proactiva se define como la TDM realizada periódicamente de forma rutinaria, independientemente del estado clínico del paciente. Aunque alguna sociedad científica como la Gastroenterological Society of Australia (GESA) se posiciona a favor de la TDM proactiva de anti-TNF[8], esta estrategia aún no está recomendada en las guías de algunas de las principales sociedades científicas, como el National Institute for Health and Care Excellence of United Kingdom (NICE)[9] y la American Gastroenterological Association (AGA)[10]. Estas sociedades aún no consideran la última evidencia disponible y por ahora recomiendan únicamente la TDM en caso de falta de respuesta en aquellos pacientes que respondieron inicialmente al tratamiento.

En el momento de iniciar en nuestro Centro el programa de monitorización de medicamentos anti-TNF, infliximab y adalimumab, ésta era una práctica relativamente

novedosa, con lagunas de conocimiento en relación con su idoneidad y utilidad en la práctica clínica. Así, iniciamos el trabajo con una revisión bibliográfica a fin de extraer datos de evidencia científica que nos permitieran implementar el programa de monitorización con seguridad[11]. Se revisaron todos los aspectos que deben ser considerados en la TDM para asegurar la utilización óptima de este recurso. En el caso concreto de los anti-TNF en EII, nos centramos en tres aspectos fundamentales: 1. Farmacocinética/Farmacodinamia (PK/PD) de anti-TNF; 2. Técnicas analíticas para la determinación del fármaco y sus anticuerpos; 3. Aspectos prácticos de la monitorización.

Uno de los objetivos de la PK es identificar las variables que condicionan los parámetros cinéticos y que explican la variabilidad inter e intraindividual y, en consecuencia, la variabilidad en la respuesta. La variabilidad PK de los anti-TNF tiene su origen en distintos factores demográficos y fisiopatológicos, como la edad, el sexo y la masa corporal. También se ha demostrado que una elevada carga inflamatoria se correlaciona con peor respuesta clínica y además se asocia con concentraciones del fármaco reducidas y con la necesidad de administrar dosis más altas en la fase de inducción[12]. Otro factor que modifica sustancialmente el aclaramiento (CL) de estos fármacos es la hipoalbuminemia. La evidencia disponible indica que pacientes con bajas concentraciones de albúmina sérica presentan mayor eliminación del fármaco. Este hecho es debido probablemente a una mayor exposición del fármaco a la degradación proteolítica como consecuencia de una menor expresión del receptor neonatal o de Brambell (FcRn)[13]. No obstante, el principal factor que incrementa sustancialmente la eliminación de estos fármacos y por lo tanto se asocia a concentraciones muy bajas o indetectables del mismo, es la presencia de AAF[3-6]. Por ello, una reducción de las concentraciones plasmáticas del fármaco anti-TNF junto con la detección de AAF puede alertar sobre una pérdida de respuesta originada por la presencia de AAF.

Dadas estas características de los fármacos anti-TNF, la TDM puede resultar de gran utilidad para la optimización posológica de los tratamientos. Esta estrategia de control terapéutico permite programar la posología de acuerdo a las características del paciente con el fin de mantener las concentraciones del fármaco dentro de los márgenes terapéuticos donde la probabilidad de eficacia sea mayor, y la probabilidad de toxicidad y de desarrollo de inmunogenicidad sea mínima. Así, se han propuesto márgenes terapéuticos de referencia para estos medicamentos en el tratamiento de la EII.

Los márgenes terapéuticos para concentraciones mínimas (Cmin) en fase de mantenimiento, se han fijado en función del objetivo terapéutico. Algunos autores han asociado Cmin entre 3-10 µg/mL para infliximab y entre 5-10 µg/mL para adalimumab con respuesta clínica sostenida[14-16]. Sin embargo, cuando el objetivo terapéutico es la respuesta endóscópica con curación mucosa o es necesaria la monoterapia con biológico, las Cmin recomendadas son ligeramente superiores: 5-10 µg/mL y 8-14 µg/mL para infliximab y adalimumab respectivamente[17,18]. Para el control de la enfermedad perianal fistulizante se han sugerido incluso Cmin de infliximab superiores a 10 µg/mL[19]. Asimismo, se ha demostrado una asociación entre las Cmin situadas dentro del margen terapéutico y la normalización de biomarcadores inflamatorios[14-18].

Para la fase de inducción del tratamiento, sin embargo, no existe evidencia robusta del margen terapéutico de concentraciones deseable para estos fármacos, aunque hay autores que afirman que previsiblemente serán necesarias concentraciones más elevadas para conseguir la respuesta primaria más adecuada y reducir la probabilidad de aparición de AAF[20,21]. El valor y utilidad de la TDM en la fase de inducción, por lo tanto, aún no está perfectamente esclarecido, aunque sí se ha constatado que el mantenimiento de concentraciones elevadas del fármaco en esta fase del tratamiento se asocia con resultados terapéuticos positivos a corto y largo plazo, mientras que las concentraciones bajas y la presencia de AAF se asocian con pérdida de respuesta y suspensión del tratamiento[20,21].

La implementación de la monitorización de estos fármacos supone un desafío en la práctica clínica diaria, en gran medida debido a la falta de estandarización de los métodos analíticos para la determinación de las concentraciones del fármaco y de sus anticuerpos[11,22]. Entre las técnicas disponibles se encuentran el ensayo por inmunoabsorción ligado a enzima (ELISA), el radioinmuensayo (RIA), el ensayo por movilidad variable (HMSA), el ensayo con gen reportero y el enzimoinmunoanálisis (EIA)[23]. Más recientemente se han desarrollado técnicas cromatográficas, como la cromatografía líquida de alta eficacia acoplada a un espectrómetro de masas (HPLC-MS/MS) para la cuantificación de infliximab[24].

Se han realizado diversos estudios comparativos entre las diferentes técnicas disponibles para la cuantificación de estos fármacos biológicos[25]. Aunque existe correlación entre las concentraciones obtenidas por los diferentes métodos, los valores absolutos pueden diferir significativamente por lo que es aconsejable que los pacientes sean monitorizados siempre en el mismo laboratorio.

El ensayo por ELISA es la técnica analítica más utilizada y fácil de implementar en la práctica clínica rutinaria debido a su alta sensibilidad y bajo coste, por lo que fue la seleccionada en nuestro Centro. Sin embargo, esta técnica presenta una serie de limitaciones que deben ser tenidas en cuenta a la hora de interpretar los resultados[23,26]. En primer lugar, se trata de una técnica *drug sensitive*, es decir, no permite la detección de los AAF en presencia de fármaco libre[22,23]. Por tanto, a diferencia de las técnicas denominadas *drug tolerant*, la detección de AAF sólo es posible cuando existen títulos altos y, por ello, un alto aclaramiento del fármaco. Por otra parte, esta técnica no es capaz de determinar anticuerpos monoméricos tipo IG4[27] ya que este tipo de inmunoglobulinas son funcionalmente monovalentes y por lo tanto no pueden unirse al conjugado del reactivo. Estas características hacen que la técnica ELISA presente un alto porcentaje de falsos negativos de AAF. La existencia de estos falsos negativos no tiene relevancia clínica, debido a que en la toma de decisiones clínicas únicamente son

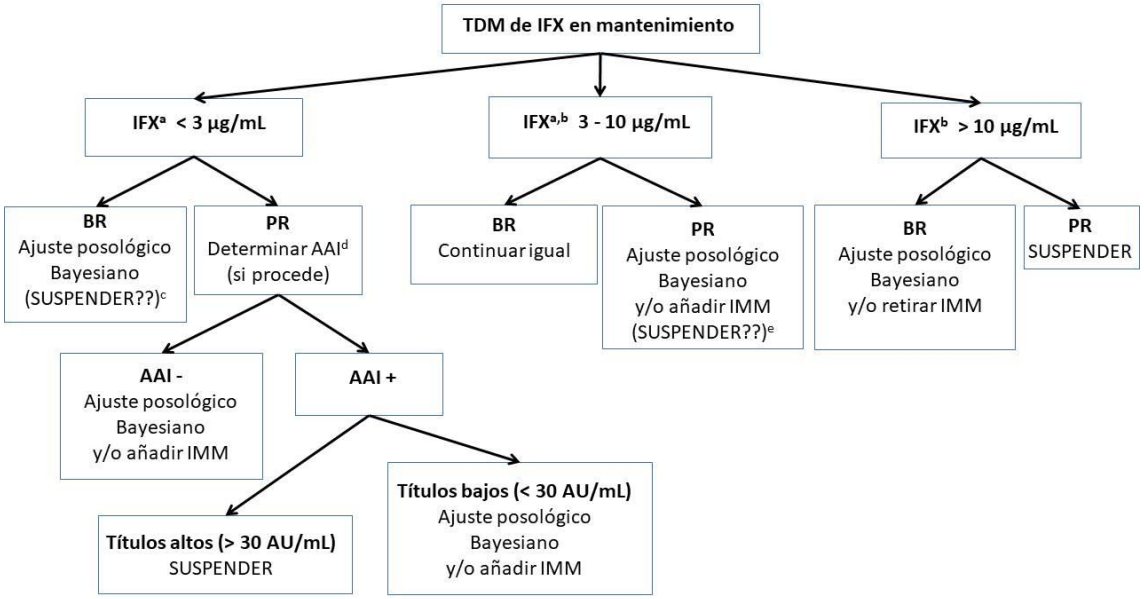
importantes los AAF en aquellos pacientes que presentan un elevado título, y estos valores elevados sí son detectables mediante un ensayo sensible al fármaco[28]. A la hora de interpretar los resultados de la determinación de AAF hay que considerar que no se dispone de estándares universales y los resultados de la concentración de AAF no son comparables entre los diferentes métodos analíticos[23]. Es necesario tener en cuenta este hecho a la hora de aplicar los diferentes algoritmos de decisión en TDM, donde es habitual encontrar términos ambiguos, como valor de AAF bajo, medio o alto, cuya clasificación depende del laboratorio de análisis[11].

En la revisión bibliográfica llevada a cabo en nuestro primer trabajo, se constató una creciente evidencia en relación a los mejores resultados clínicos asociados a las estrategias de TDM proactiva llevada a cabo en pacientes en fase de mantenimiento[17,29]. No obstante, hasta ese momento, la mayoría de los algoritmos de decisión basados en las concentraciones del fármaco y sus anticuerpos se habían desarrollado para el manejo de la pérdida de respuesta[15]. Según dichos algoritmos, ante una pérdida de respuesta los pacientes que presentan concentraciones del anti-TNF infraterapéuticas y AAF no detectables, se benefician más de un incremento de la dosis que del cambio a un fármaco de otro mecanismo de acción. Sin embargo, aquellos con concentraciones elevadas de anti-TNF, responden mejor a un cambio a otro fármaco con distinto mecanismo de acción que a un incremento de la dosis.

Fruto de la revisión bibliográfica realizada y, considerando las potenciales ventajas de la estrategia de monitorización proactiva, en nuestro Centro se optó por diseñar nuevos algoritmos para su aplicación en la fase de mantenimiento y en la post-inducción temprana de infliximab en semana 14[11,30]. Dichos algoritmos aparecen recogidos en nuestro primer trabajo y fueron utilizados al comienzo de la implementación de la TDM de anti-TNF. Posteriormente, considerando nuestra experiencia acumulada y tras desarrollar modelos farmacocinéticos propios para infliximab y adalimumab, los protocolos y algoritmos de monitorización fueron actualizados. Las figuras 1 y 2

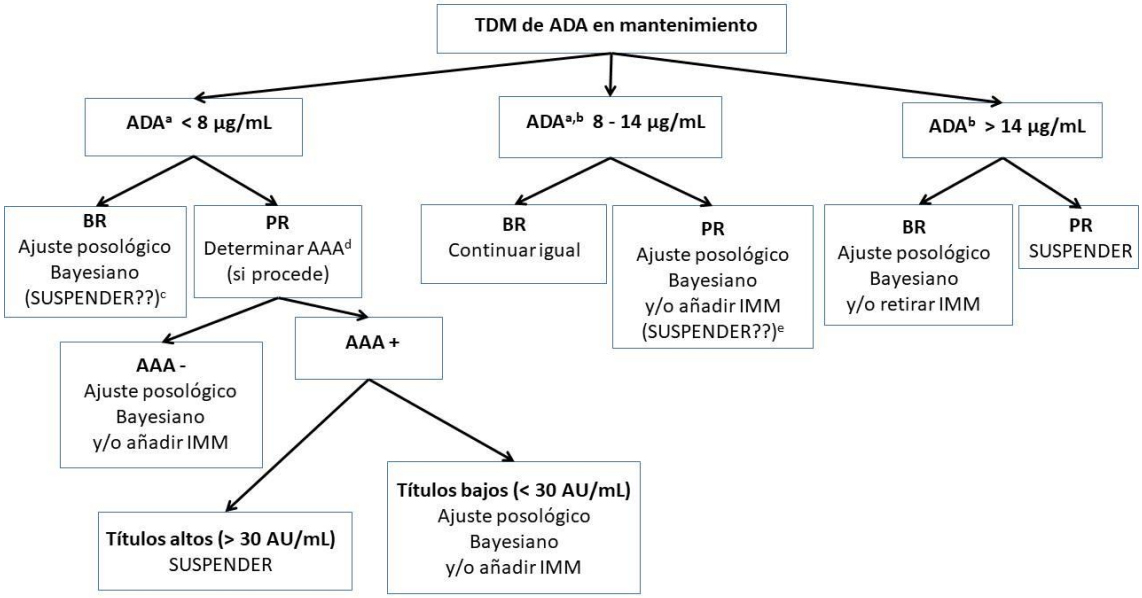
muestran nuestra recomendación para el manejo integral del paciente durante la fase de mantenimiento del tratamiento con infliximab o adalimumab, mientras que las figuras 3 y 4 se incluyen los nuevos algoritmos incorporados en el Centro donde se incluye la optimización temprana durante la fase de inducción del tratamiento en pacientes tratados con estos fármacos.

Nuestra experiencia, además, nos ha permitido identificar pacientes candidatos a ser monitorizados más estrechamente durante la fase de inducción, entre los que se encuentran aquellos tratados en monoterapia con anti-TNF, con alta carga inflamatoria (definida como calprotectina fecal (FC) superior a 400 mg/Kg) y aquellos con un brote moderado o grave de colitis ulcerosa extensa (pancolitis). Asimismo, la aplicación de la PK poblacional y empleando los modelos desarrollados permite personalizar la inducción del tratamiento. De hecho, se han identificado situaciones que requieren dosis intensificadas desde el inicio de tratamiento. Así, por ejemplo, en pacientes con pancolitis graves y con alta carga inflamatoria (CF > 400 mg/Kg), se recomienda una primera dosis de 10 mg/Kg y un primer control de TDM en la semana 1.



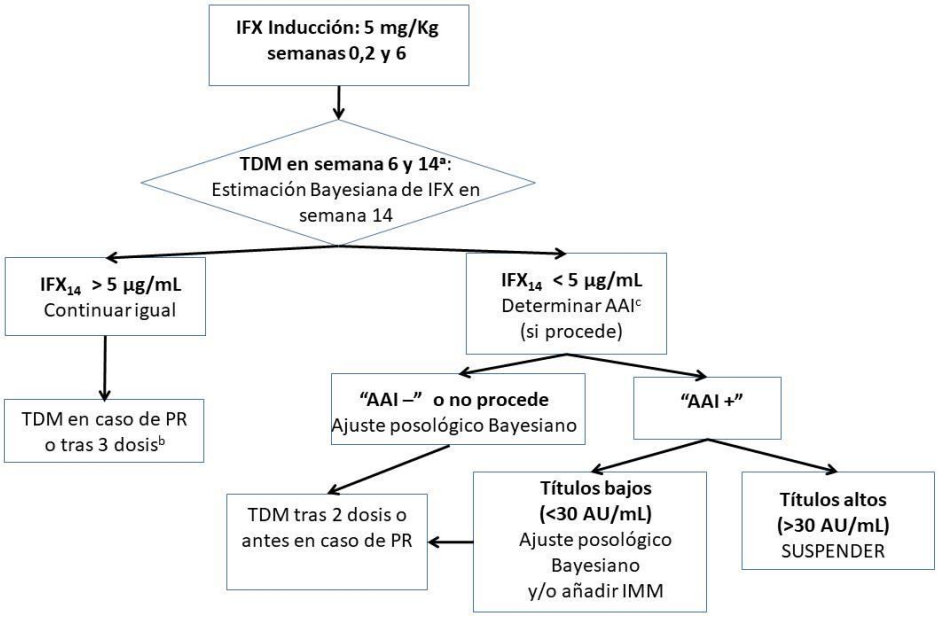
AAI: anticuerpos anti-infliximab; BR: buena respuesta; IFX: infliximab; IMM: inmunosupresores; PR: pérdida de respuesta; TDM: monitorización farmacocinética.
a: 5 µg/mL en monoterapia con infliximab.
b: 10-15 µg/mL en enfermedad de Crohn perianal fistulizante.
c: pacientes con curación mucosa durante un largo periodo de tiempo y concentraciones mínimas infra-terapéuticas de IFX podrían ser candidatos a descanso terapéutico.
d: sólo si se dispone de una técnica drug sensitive. En otro caso, interpretar AAI según las especificaciones del ensayo.
e: pacientes con concentraciones mínimas en el límite superior del margen terapéutico probablemente no se beneficien de intensificar el tratamiento.

Figura 1. Algoritmo de decisión basado en las concentraciones séricas mínimas de infliximab, la presencia de anticuerpos anti-infliximab y la respuesta al tratamiento. La evaluación de la respuesta se basa en resultados clínicos, endoscópicos y bioquímicos.



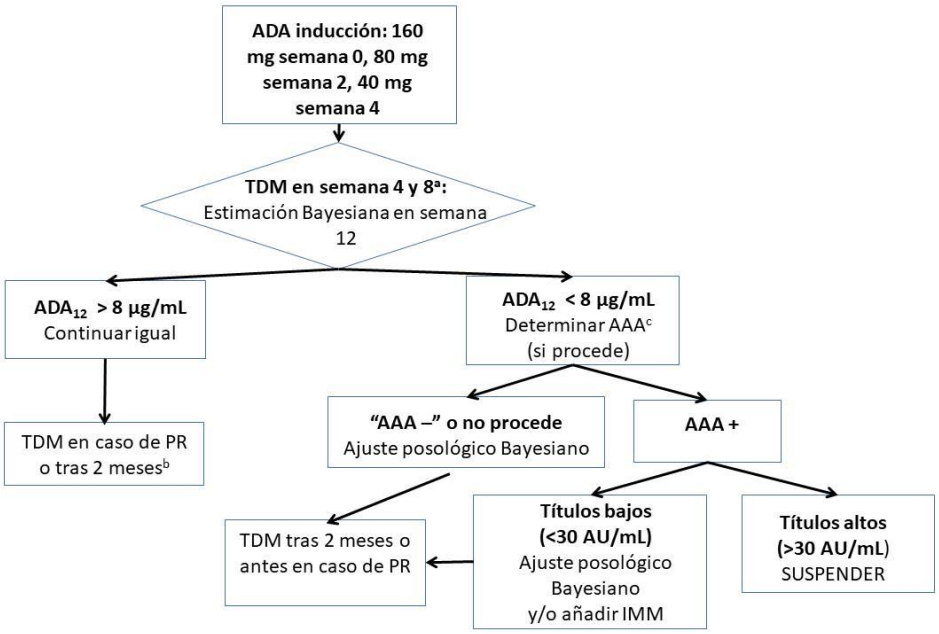
AAA: anticuerpos anti-adalimumab; ADA: adalimumab; BR: buena respuesta; IFX: infliximab; IMM: inmunosupresores; PR: pérdida de respuesta; TDM: monitorización farmacocinética.
a: 5 µg/mL si el objetivo terapéutico es conseguir respuesta clínica.
b: 12-20 µg/mL en enfermedad de Crohn perianal fistulizante.
c: pacientes con curación mucosa durante un largo periodo de tiempo y concentraciones mínimas infra-terapéuticas de ADA podrían ser candidatos a descanso terapéutico.
d: sólo si se dispone de una técnica drug sensitive. En otro caso, interpretar AAA según las especificaciones del ensayo.
e: pacientes con concentraciones mínimas en el límite superior del margen terapéutico probablemente no se beneficien de intensificar el tratamiento.

Figura 2. Algoritmo de decisión basado en las concentraciones séricas mínimas de adalimumab, la presencia de anticuerpos anti-adalimumab y la respuesta al tratamiento. La evaluación de la respuesta se basa en resultados clínicos, endoscópicos y bioquímicos.



AAI: anticuerpos anti-infliximab; IFX: infliximab; IFX: infliximab; $IFX_{14:}$ concentración estimada de IFX en semana 14 ; IMM: inmunosupresores; PR: pérdida de respuesta; TDM: monitorización farmacocinética.
a: TDM adicional en la semana 2 en pacientes con alto riesgo de fracaso primario: IFX en monoterapia, alta carga inflamatoria (calprotectina fecal > 400 mg/Kg), pancolitis o historial de anticuerpos frente a otro anti-TNF.
b: después de 2 administraciones en pacientes en tratamiento con IFX en monoterapia.
c: sólo si se dispone de una técnica drug sensitive. En otro caso, interpretar AAI según las especificaciones del ensayo..

Figura 3. Algoritmo de monitorización proactiva de infliximab durante la fase de inducción del tratamiento con ajuste posológico utilizando estimación Bayesiana. La evaluación de la respuesta se basa en resultados clínicos, endoscópicos y bioquímicos.



AAA: anticuerpos anti-adalimumab; ADA: adalimumab; $ADA_{12:}$ concentración estimada de ADA en semana 12 ; IMM: inmunosupresores; PR: pérdida de respuesta; TDM: monitorización farmacocinética.
a: TDM adicional en la semana 2 en pacientes con alto riesgo de fracaso primario: ADA en monoterapia, alta carga inflamatoria (calprotectina fecal > 400 mg/Kg), pancolitis o historial de anticuerpos frente a otro anti-TNF.
b: después de un mes en pacientes en tratamiento con ADA en monoterapia. o historial de anticuerpos frente a otro anti-TNF
c: sólo si se dispone de una técnica drug sensitive. En otro caso, interpretar AAA según las especificaciones del ensayo.

Figura 4. Algoritmo de monitorización proactiva de adalimumab durante la fase de inducción del tratamiento con ajuste posológico utilizando estimación Bayesiana. La evaluación de la respuesta se basa en resultados clínicos, endoscópicos y bioquímicos.

La optimización posológica de los tratamientos farmacológicos mediante TDM exige disponer de ecuaciones poblacionales (PopPK) que nos permitan interpretar los datos obtenidos en la monitorización y estimar los parámetros PK individualizados en los cuales se basará la dosificación personalizada. Al inicio del programa de TDM de estos fármacos, utilizamos los modelos PopPK disponibles en la bibliografía y la optimización posológica se abordó utilizando un enfoque Bayesiano[31]. Según esta metodología, la información *a priori* (parámetros farmacocinéticos poblacionales) se combinó con información *a posteriori* (concentraciones de anti-TNF determinadas en los pacientes a distintos tiempos) para predecir las concentraciones futuras del fármaco. Esta

información, junto con los resultados clínicos, bioquímicos y endoscópicos, se utilizó para elaborar un informe farmacocinético con la recomendación de dosis personalizada para cada paciente.

En nuestra revisión bibliográfica encontramos varios modelos PopPK que trataban de caracterizar la PK de infliximab y adalimumab[32-37]. Sin embargo, estos modelos no evaluaron el impacto sobre el comportamiento cinético de los biomarcadores inflamatorios introducidos recientemente en clínica, como la CF. Este marcador, hoy en día, es ampliamente utilizado para evaluar la situación clínica del paciente y la respuesta al tratamiento. Una vez que dispusimos de suficientes datos de pacientes, recogidos en vida real, abordamos los análisis poblacionales pertinentes para obtener nuestros propios modelos PopPK para adalimumab e infliximab. Durante el desarrollo de los mismos se analizó no solo el impacto de distintos parámetros fisiológicos sino también el de los biomarcadores habitualmente utilizados en el diagnóstico y seguimiento de la enfermedad.

El estudio poblacional de adalimumab se llevó a cabo con los datos de 124 pacientes (104 para el desarrollo del modelo PopPK y 20 para la validación) diagnosticados tanto de enfermedad de Crohn (EC) como de colitis ulcerosa (CU) durante un periodo de 3 años. Las concentraciones se describieron adecuadamente siguiendo un modelo abierto monocompartimental con absorción y eliminación de primer orden. El CL del fármaco estaba significativamente afectado por el índice de masa corporal (IMC), el dispositivo de administración (pluma de 40 o de 80 mg), la CF y la sospecha de inmunogenicidad. No se encontraron diferencias estadísticamente significativas en el comportamiento PK entre los pacientes diagnosticados de EC y CU.

En la tabla 1 se recogen las especificaciones de los modelos PopPK de adalimumab disponibles actualmente, junto con las principales características de nuestro modelo[38]. En nuestro modelo, a diferencia de otros publicados anteriormente que incluían el peso corporal como covariable, el IMC fue el parámetro antropométrico con impacto más

significativo sobre el CL, incrementándose con el IMC. El tejido adiposo es un tejido de alta actividad metabólica e inmunogénica[39]. El hecho de que los pacientes con mayor cantidad de tejido adiposo, y por lo tanto mayor IMC, presenten menores concentraciones de fármaco podría estar relacionado con una mayor degradación presistémica y menor biodisponibilidad[40]. Por otra parte, encontramos una influencia significativa del dispositivo de administración en la exposición al adalimumab. Una de las desventajas de la administración subcutánea de inmunoglobulinas es su metabolismo presistémico[41,42]. En nuestro caso encontramos que el uso de la pluma de 80 mg podría dar lugar a concentraciones inferiores a las que cabría esperar tras la administración de dos plumas de 40 mg. Esto probablemente es debido a una biodisponibilidad no lineal y dependiente de la dosis.

Tabla 1. Características de los modelos farmacocinéticos poblacionales actualmente disponibles para adalimumab.

	Ternant el al. 2015[34]	Berends et al. 2018[35]	Vande Castelee et al. 2019[36]	Sánchez-Hernández et al. 2020[38]
Tipo de estudio	Retrospectivo	Retrospectivo	Prospectivo	Prospectivo
Enfermedad	EC	EC	EC	EC y CU
Nº Pacientes	65	96	28	104
Técnica analítica para determinar AAA	ELISA de doble antígeno (*drug sensitive*).	ELISA de doble antígeno (*drug sensitive*).	ELISA *in house* (*drug tolerant*)	ELISA de doble antígeno (*drug sensitive*).
Covariables estudiadas	AAA	Edad, sexo, PT AAA, anti-TNF previos, albumina, PCR, immunomoduladores concomitantes, Actividad clínica, régimen de dosificación (semanal/ quincenal) y fase de tratamiento.	Edad, sexo, PT, IMC, SC, PI, AAA, albumina, PCR, Hb, HBI, s-TNF y s-TNFR-1	Edad, sexo, PT, IMC, SC, PI, PIA, sospecha de AAA, tipo de enfermedad, localización anatómica, comportamiento (EC), edad al diagnóstico, edad al inicio de tratamiento, EPA, immunomoduladores concomitantes, manifestaciones extraintestinales, albúmina, CF, PCR, dispositivo de administración y anti-TNF previos.
	Estimado (% ERS)	**Estimado (% ERS)**	**Estimado (% ERS)**	**Estimado (% ERS)**
CL/F (L/d)	0,42 (9)	0,32 (8)	0,33 (0)	0,38 (3)
V/F (L)	13,5 (10)	4,1 (27)	7,8 (0)	11,2 (9)
Ka (1/d)	0,15	0,20 (fijo)	0,34 (0)	0,15 (fijo)
AAA-CL	4,50	3,14 (24)	1,59 (18)	1,20 (28)
Covariables sobre CL	-	AAA, Dosificación semanal.	AAA, PI	Sospecha de AAA, IMC, CF y dispositivo de administración.
Covariables sobre V	-	-	-	-
IIV-CL/F (%)	64,8 (10)	49,1 (12)	32,6 (0)	23,2 (9)
IIV-V/F (%)	48 (19)	-	35,6 (0)	-
Error residual proporcional	0,15 (16)	0,30 (9)	0.028 (0)	0,047 (13)
Error residual aditivo (mg/L)	1,8 (8)	1,02 (23)	-	-

AAA: anticuerpos anti-adalimumab; CF: calprotectina fecal; CL/F: aclaramiento aparente; CU: colitis ulcerosa; EC: enfermedad de Crohn; EPA: enfermedad perianal; ERS: error residual estándar; ES: error estándar; Hb: hemoglobina sérica; HBI: índice de Harvey Bradshaw; Ka: constante de absorción; IIV: variabilidad interindividual; IMC: índice de masa corporal; PCR: proteína-C reactiva; PI: peso corporal ideal; PIA: peso corporal ideal ajustado; PT: peso corporal total; SC: superficie corporal; s-TNF: factor de necrosis tumoral soluble; s-TNFR-1: receptor soluble del factor de necrosis tumoral; V/F: volumen aparente de distribución.

Una de las principales novedades de nuestro modelo es la inclusión de la CF como covariable del CL. En estudios anteriores, la proteína C reactiva (PCR) y la albúmina fueron los biomarcadores inflamatorios con mayor influencia sobre la eliminación de adalimumab[37]. Sin embargo, la inclusión de la CF en nuestro modelo nos permite una mejor estimación del CL de adalimumab que la PCR y la albúmina. Este hallazgo tiene gran relevancia clínica, dado que la CF es un parámetro no invasivo y su uso en la práctica clínica está cada vez más extendido ya que estudios recientes han demostrado que la CF es un marcador que se correlaciona bien con la actividad endoscópica y la respuesta terapéutica[43]. Además, resulta útil en la predicción de la recaída y la recurrencia postoperatoria en la CU y en la EC colónica e ileocolónica[43,44]. De hecho, para este fin, la CF ha mostrado ser un marcador con mayor poder de predicción que la PCR y otros biomarcadores fecales[43]. Existe controversia de la utilidad de este biomarcador en EC de localización exclusivamente ileal[44], aunque recientemente se han realizado estudios que sugieren que la CF es un marcador fiable de actividad endoscópica ileal, aunque menos relevante que en la enfermedad colónica[45,46].

Por último, debido a las limitaciones de la técnica ELISA respecto a la determinación de AAF comentadas anteriormente, se ha definido la covarible “sospecha de anticuerpos” como una disminución en las concentraciones del fármaco sin ninguna causa aparente: buena adherencia confirmada, sin cambios significativos en los marcadores bioquímicos y clínicos; y reversible con aumento de la dosis del fármaco. Este parámetro permite, utilizando una estrategia proactiva de TDM, identificar pacientes en fase temprana de inicio de inmunogenicidad antes de manifestarse en concentraciones infraterapéuticas o indetectables que pueden estar asociadas con pérdida de respuesta al tratamiento.

Tal y como se observa en la tabla 1, nuestro modelo PopPK de adalimumab, caracteriza adecuadamente el comportamiento cinético del fármaco y permite explicar la variabilidad interindividual en el CL en mayor medida que otros modelos previos. La menor variabilidad interindividual en este parámetro (23%) puede atribuirse al hecho de

haber identificado nuevas variables con influencia en la eliminación del fármaco. Por lo tanto, nuestro modelo podría resultar más adecuado para diseñar *a priori* un régimen posológico personalizado de inicio en función de las características particulares que presente el paciente.

De manera similar al desarrollo del modelo PopPK de adalimumab, hemos desarrollado un modelo preliminar para infliximab con 313 datos de concentraciones séricas correspondientes a 108 pacientes con EII[30]. Para este fármaco, el comportamiento cinético se describe mediante un modelo bicompartimental de eliminación de orden uno. En este caso, el peso corporal, la CF y la presencia de anticuerpos anti-infliximab demostraron ser las variables con impacto más significativo sobre la PK de infliximab. Este modelo inicial describe adecuadamente el comportamiento cinético del fármaco, y ha sido utilizado con éxito en nuestro programa de monitorización. Sin embargo, la experiencia acumulada y los nuevos datos de monitorización de que disponemos nos han llevado a rediseñar el modelo PopPK , lo que permitirá determinar con mayor precisión todos los factores que afectan a la PK de infliximab, incluida la asociación con inmunosupresores clásicos como la azatioprina. En este momento nos encontramos en la fase inicial del análisis por lo que sería prematuro extraer conclusiones.

Finalmente, se realizó un estudio para valorar los resultados clínicos obtenidos a largo plazo con la monitorización proactiva de infliximab en nuestro Centro, con el fin de evaluar la utilidad del programa. Previamente, al inicio del mismo, se cuantificó la prevalencia de Cmin terapéuticas de infliximab en los pacientes en tratamiento activo en ese momento. Se incluyeron un total de 52 pacientes cuya dosificación había sido optimizada empíricamente según la respuesta al tratamiento. Los resultados obtenidos mostraron un bajo porcentaje de pacientes con Cmin dentro del margen terapéutico (40%). Además, se detectaron anticuerpos anti-infliximab en un gran número de pacientes (14%), lo que probablemente está relacionado con el alto porcentaje de pacientes (48%) con Cmin por debajo del margen terapéutico. Nuestro estudio también

mostró que la respuesta terapéutica obtenida estaba directamente relacionada con la magnitud de la concentración sérica alcanzada. De hecho, mientras que en el grupo que presentaba Cmin infraterapéuticas (<3 µg/mL) solamente habían obtenido buena respuesta el 52% de los pacientes, esta proporción era del 76% en aquellos pacientes con concentraciones terapéuticas (3-10 µg/mL). Estos hallazgos apoyan la conveniencia de guiar las decisiones terapéuticas en base a los resultados de la monitorización con el fin de individualizar la posología para alcanzar unas concentraciones adecuadas y mejorar los resultados terapéuticos.

Para evaluar los resultados en salud de la TDM proactiva de inflximab, se realizó un estudio observacional prospectivo de 3 años de duración. Los resultados del estudio prospectivo se compararon con los obtenidos retrospectivamente en todos los pacientes que habían recibido infliximab en los tres años anteriores, y que habían recibido dosificación empírica según la respuesta clínica observada, opción considerada el estándar de tratamiento hasta ese momento. En el estudio prospectivo, los pacientes recibieron dosis individualizadas de acuerdo a las Cmin de infliximab determinadas de forma proactiva desde la semana 14 del inicio del tratamiento. Hasta disponer de nuestro propio modelo PopPK utilizamos los modelos farmacocinéticos disponibles en la bibliografía y la optimización posológica se abordó utilizando un enfoque Bayesiano como se ha descrito previamente. Esta información, junto con los resultados clínicos y endoscópicos, se utilizó para elaborar un informe farmacocinético con la recomendación de dosis adaptada al paciente.

Al analizar los resultados de este estudio, se observó que en los pacientes con TDM proactiva, la probabilidad de fracaso del tratamiento era del 23% a los tres años. Esta probabilidad fue significativamente menor ($p < 0,05$) que la obtenida en el grupo control (46%). Además, los riesgos de cirugía y hospitalización relacionados con la enfermedad se redujeron significativamente ($p<0,05$) en el grupo de estudio, reduciéndose el riesgo de cirugía del 28% al 3% y el de hospitalización del 32% a 9%. Respecto a la seguridad

de los tratamientos, se encontró una menor incidencia de reacciones infusionales graves en el grupo de estudio (2,5%) respecto al grupo control (10,4%). Estos resultados podrían estar relacionados con la baja proporción de pacientes en los que se detectaron anticuerpos anti-infliximab positivos (4,9 %) en el grupo de estudio, ya que existe evidencia de que éstos puede activar la vía del complemento y la producción de anafilotoxinas[47]. Sin embargo, la incidencia de otros tipos de reacciones adversas fue similar en ambos grupos.

La personalización del tratamiento mediante la TDM, va dirigido a maximizar los beneficios terapéuticos del tratamiento, objetivo que nuestra estrategia de monitorización nos ha permitido alcanzar. Los resultados encontrados, mayor durabilidad de los tratamientos, reducción del riesgo de cirugía, hospitalización y aparición de reacciones infusionales graves graves, apoyan la conveniencia de guiar las decisiones terapéuticas de acuerdo a los resultados de la monitorización proactiva. Los resultados obtenidos son acordes a los observados en diferentes estudios previos llevados a cabo en pacientes en tratamiento con infliximab y TDM proactiva[18,48,49]. Todos estos estudios presentaban los inconvenientes de la falta de randomización de los pacientes y el carácter retrospectivo. Sin embargo, nuestro estudio está basado en datos prospectivos, obtenidos de la práctica clínica real y no están sesgados respecto a la selección de pacientes ya que se incluyeron todos aquellos que iniciaron infliximab en el Centro. En este sentido, nuestros datos aportan mayor evidencia en relación al beneficio clínico de la monitorización proactiva de infliximab[31,49]. Asimismo, en el caso de adalimumab recientemente se ha publicado un estudio donde se encontraron mejores resultados terapéuticos en pacientes bajo una estrategia proactiva de monitorización frente a un manejo reactivo por respuesta clínica[50].

Por otro lado, entre las limitaciones del estudio están la no aleatorización de los pacientes y el uso de una población histórica como grupo de control. Por tanto, los resultados deberían confirmarse mediante un ensayo prospectivo aleatorizado y

controlado. No obstante, aunque esto se considera el *gold standard* del diseño de un estudio, está limitado por varios factores, como los recursos, el alto coste o incluso estándares éticos. Además, tal y como se comentó, en el análisis de concentraciones-respuesta previo al inicio del programa de monitorización se observó un alto porcentaje de pacientes con Cmin infraterapéuticas, que se asociaron con una pobre respuesta al tratamiento. Teniendo en cuenta estos resultados, junto con la evidencia disponible en la bibliografía, no se consideró ético utilizar como comparador un grupo control de manejo posológico empírico.

Aunque los gastroenterólogos utilizan rutinariamente la TDM de los medicamentos biológicos anti-TNF, los resultados de algunos estudios y datos de algunas encuestas sugieren la necesidad de contar con una guía para la adecuada interpretación de los resultados obtenidos y ayuda en la toma de decisiones[51-53]. El desarrollo de nuestro programa de monitorización farmacocinética de anti-TNF ha sido fruto de la colaboración entre los Servicios de Farmacia Hospitalaria y de Aparato Digestivo. Tras el análisis de las concentraciones de anti-TNF e interpretación de las mismas, se realiza el informe farmacocinético y recomendación posológica, información que es evaluada conjuntamente con el facultativo responsable del paciente, programando las actuaciones posteriores en función de esta información y la situación clínica del paciente. Aunque no es posible afirmar que los resultados positivos encontrados puedan atribuirse al carácter multidisciplinar de la atención integral del paciente, sí queremos resaltar que en nuestra experiencia la implicación del experto en PK clínica ha contribuido de manera decisiva en la consecución de los resultados positivos del programa. Cabe además señalar que el trabajo en equipos multidisciplinares se considera una buena práctica dentro del sistema sanitario[54]. Esto implica una coordinación de esfuerzos entre diferentes especialistas con experiencia en sus áreas correspondientes, siendo la combinación de sus habilidades un aspecto clave para ayudar a mejorar los resultados en salud.

En conclusión, la dosificación empírica de anti-TNF según respuesta terapéutica en pacientes con EII se asocia con un alto porcentaje de pacientes con Cmin infraterapéuticas y desarrollo de AAF. Nuestro programa de TDM proactiva después de la fase de inducción mejora los resultados a largo plazo: aumenta la persistencia de estos medicamentos, disminuye la hospitalización y la cirugía relacionadas con la enfermedad, y se reduce la inmunogenicidad y las reacciones infusionales graves. Por lo tanto, nuestros resultados apoyan el uso de la TDM proactiva y, según nuestra experiencia, la atención multidisciplinar es un enfoque útil para personalizar la terapia con anti-TNF en pacientes con EII.

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V. CONCLUSIONES

I. La monitorización farmacocinética de anti-TNF ofrece un enfoque racional para la optimización de las terapias en enfermedad inflamatoria intestinal. Existe cada vez mayor evidencia de la correlación entre las concentraciones de estos fármacos y los resultados clínicos. La implementación de algoritmos terapéuticos proactivos integrando la respuesta clínica con la monitorización farmacocinética está ganando creciente aceptación en la práctica clínica.

II. Se ha desarrollado y validado un modelo farmacocinético poblacional de adalimumab que caracteriza adecuadamente el comportamiento cinético del fármaco en pacientes con enfermedad inflamatoria intestinal. El índice de masa corporal, la calprotectina fecal, el dispositivo de administración y la sospecha de anticuerpos se han identificado como principales variables con influencia significativa en el aclaramiento y exposición al fármaco. Este modelo podría ser una herramienta útil tanto para la detección precoz del desarrollo de inmunogenicidad como para la individualización de la dosis del fármaco lo que redundaría en una mayor eficacia y seguridad de estos tratamientos.

III. Se ha desarrollado y validado un modelo farmacocinético poblacional de infliximab que caracteriza adecuadamente el comportamiento cinético del fármaco en pacientes con enfermedad inflamatoria intestinal en fase de mantenimiento. La presencia de anticuerpos anti-infliximab, el peso y la calprotectina fecal se han identificado como principales variables con influencia significativa en el aclaramiento y exposición al fármaco.

IV. El ajuste posológico empirico de infliximab según respuesta terapéutica conduce a un alto número de pacientes con concentraciones míminas infraterapéutcas, mayores tasas de anticuerpos y peores resultados clínicos.

V. La implantación de un programa de monitorización proactiva de infliximab en enfermedad inflamatoria intestinal en nuestro Centro ha mejorado los resultados clínicos a medio y largo plazo:

- Aumenta la durabilidad del tratamiento.
- Disminuye las tasas de hospitalización y cirugía relacionadas con reagudización o brote de la enfermedad.
- Reduce la inmunogenicidad y las reacciones infusionales moderadas/ graves, mejorando la seguridad de los tratamientos.

VI. Nuestra experiencia en la aplicación de la farmacocinética poblacional, junto con la utilización de los modelos farmacocinéticos desarrollados, ha permitido intervenir proactivamente durante la fase de inducción de los tratamientos y reducir, por lo tanto, el número de fracasos primarios a anti-TNF.

VII. Los resultados generales de nuestro programa implantado en el Hospital respaldan el uso de la monitorización proactiva y, de acuerdo a nuestra experiencia, el abordaje multidisciplinar para personalizar la terapia con infliximab en pacientes con enfermedad inflamatoria intestinal mejora considerablemente los resultados en salud.